ANNALS OF SURGERY

VOL. 130 NOVEMBER, 1949 No. 5

THE CAUSE OF DEATH IN STRANGULATION OBSTRUCTION: AN EXPERIMENTAL STUDY

I. CLINICAL COURSE, CHEMICAL, BACTERIOLOGIC AND SPECTROPHOTOMETRIC STUDIES*

PAUL NEMIR, JR., M.D., H. R. HAWTHORNE, M.D., ISIDORE COHN, JR., M.D. AND DAVID L. DRABKIN, M.D.

PHILADELPHIA, PA.

FROM THE HARRISON DEPARTMENT OF SURGICAL RESEARCH, SCHOOL OF MEDICINE, AND THE DEPARTMENTS OF SURGERY AND PHYSIOLOGICAL CHEMISTRY, GRADUATE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA

THE MORTALITY IN ACUTE intestinal obstruction has decreased from around 60 per cent at the turn of the century to 10 to 20 per cent in the larger clinics at the present time (Table I). A comparison of different series of cases from the same clinic over the period of years further demonstrates this decline—University of Pennsylvania;[7, 9, 19] Massachusetts General Hospital;[3, 4, 10, 16] Johns Hopkins Hospital;[5, 20] University of Minnesota Hospitals.[14, 18]

This decline in mortality, however, has been manifested more in cases of simple obstruction than in strangulation obstruction.[6, 16, 19] In 1947, Eliason and Welty[19] reported a mortality of only one per cent in those cases of obstruction not complicated by strangulation or carcinoma. On the other hand, even as late as 1940, Schlicke, Bargen and Dixon[17] reported a mortality of 56 per cent of those cases where gangrenous bowel was found at operation, and even more recent reports showed a mortality of 20 to 40 per cent in this group of patients.[18-20] It is of particular interest to note that although at the present time interference with the circulation occurs in only 17 to 33 per cent of the total cases,[16-20] the mortality ranges between 25 and 40 per cent, and these cases account for more than half of the total deaths reported in the various series.[16-18, 20] The continued high mortality in cases of strangulation obstruction indicates that factors other than those amenable to present improved methods of management exist in this condition.

We have investigated the problem of strangulation obstruction utilizing certain of the newer concepts of management in an attempt to further clarify the cause of death. Following the creation of a strangulated ileal obstruction in dogs, the animals were treated for hemorrhage, shock, dehydration and electrolyte loss, and studies were made on the blood, peritoneal fluid, and gut contents.

* Aided by a grant from the National Drug Co., Philadelphia, Pennsylvania. Submitted for publication April, 1949.

METHODS

Seven carefully selected, vaccinated, dewormed adult mongrel dogs weighing between 9.4 and 17.0 Kg. were used in this experiment. Following a 24 hour period of starvation, the animals were operated upon under Na pentobarbital (24.0 mg. per Kg.) anesthesia. Samples of blood for control chemical studies were taken on the day before or the morning of operation. Strict aseptic technic was used throughout. All the omentum distal to the spleen was excised in order to facilitate the withdrawal of peritoneal fluid and to obviate the omentum as a source of revascularization of the strangulated segment.[22] At a point between 100 and 150 cm. from the ligament of Trietz, the bowel was severed and the cut ends closed by the Parker-Kerr technic (Fig. 1). Fifteen centimeters above the proximal closed end a 30 cm. segment of bowel was strangulated by doubly ligating the veins in the base of the mesentery. The communicating arteries and veins at either end of the

TABLE I

Year Reported	Period Covered	Author	Hospital	No. of Cases	Mortality
					%
1888	1880–1883	Fitz[1]	Collected	146	70.0
1900	Up to 1900	Gibson[2]	Collected	1000	43.0
1908	1898–1907	Scudder[3]	Mass. General	121	60.0
1920	1908–1917	Richardson[4]	Mass. General	118	50.0
1921	1912–1921	Finney[5]	Johns Hopkins	245	36.0
1925	1900–1925	Van Buren and Smith[6]	Collected	1089	41.8
....	1914–1923	.....	Presbyterian	174	58.0
1929	1905–1922	North[7]	Univ. of Pa.	200	30.5
1925	Up to 1925	Souttar[8]	Collected	3064	32.0
1929	1922–1928	Brill[9]	Univ. of Pa.	124	36.3
1932	1918–1927	McIver[10]	Mass. General	335	31.0
1929	1924–1929	Miller[11]	Charity Touro Infir.	343	61.0
1934	1922–1932	Christopher and Jennings[12]	Evanston	127	44.9
1938	Up to 1938	Scudder[13]	Collected	2150	24.0
1938	1931–1938	Wangensteen[14]	Univ. of Minn.	156	17.9
1940	1936–1939	Johnston[15]	Wayne Univ.	63	19.1
1940	1927–1938	McKittrick and Sarris[16]	Mass. General	136	20.0
1940	1938–1939	Schlicke, Bargen and Dixon[17]	Mayo Clinic	166	22.0
1943	1938–1942	Dennis and Brown[18]	Univ. of Minn.	110	15.5
1947	1934–1943	Eliason and Welty[19]	Univ. of Pa.	292	11.0
1946	1936–1945	Calihan, Kennedy and Blain[20]	Johns Hopkins	204	20.0
1946	1943–1945	Moses[21]	Gallinger Municipal	118	8.0

strangulated segment, running parallel and adjacent to the bowel on the mesenteric border, were severed and doubly ligated. A segment of plastic tubing was threaded through normal bowel into the strangulated segment; two multiperforated latex tubes were placed in the lateral gutters; all tubes were brought out onto the anterior abdominal wall through stab wounds, and the abdomen was closed. At the conclusion of the procedure the strangulated segment was invariably dusky blue in color, and in some cases had begun already to exude a pink serous transudate.

Another segment of plastic tubing was then threaded through the jugular vein into the superior vena cava, anchored to the skin, and then connected to a gravity drip, thus enabling the animal to receive large amounts of fluids constantly while moving freely about in his cage.

Parenteral fluid administration was begun at operation and continued con-

stantly throughout the period of survival, the amount and type of fluid, *i.e.*, blood, glucose and saline or gelatin, being determined by the hematocrit and hemoglobin at two or four hour intervals and by the clinical condition of the animal. Postoperatively, usually at four hour intervals, the peritoneal cavity and gut were aspirated, and blood samples were withdrawn from the femoral artery for serial studies. In all instances all the peritoneal fluid obtainable from the latex tubes at each interval was removed under sterile conditions. In six of the seven animals, only several cubic centimeters of bowel contents were removed for chemical determinations. In the remaining animal (No. 347), the gut contents were evacuated as completely as possible at four hour intervals. Blood and peritoneal fluid cultures were taken at various intervals, and gut contents were cultured just prior to death in a number of the animals.

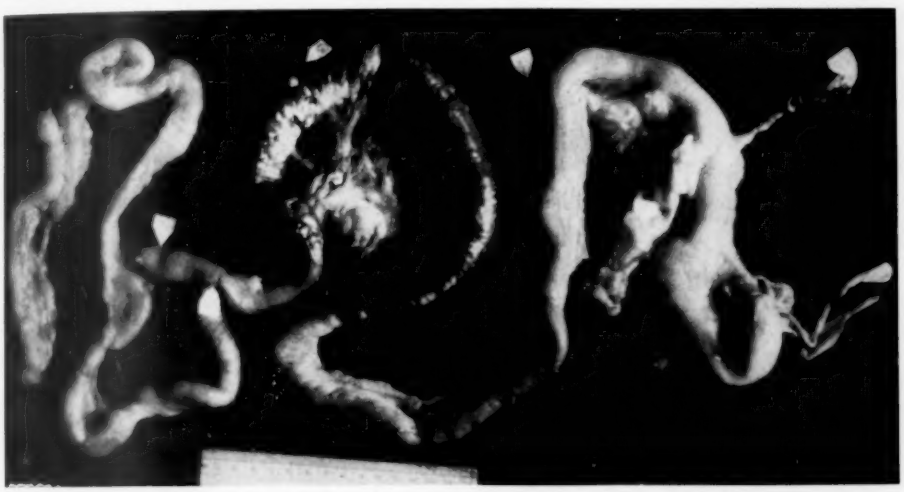


FIG. 1.—Photograph of strangulated segment of bowel from dog No. 331. The distal turned in end was sutured to the side of the proximal closed end in order to prevent intussusception. This was the usual picture noted in five of the seven dogs (see text).

The following chemical determinations were done: specific gravities;[23] proteins;[24] urea nitrogen;[25] nonprotein nitrogen;[26] creatinine;[26] uric acid;[27, 28] total nitrogen;[29] amino acid nitrogen;[30] amylase;[31] lipase;[32] chlorides;[33] calcium;[34] CO_2 combining power;[35] pH;[36] potassium[37] and spectrophotometric studies.[38*]

* The absorption spectrum curves are plots of *fractional molecular extinction coefficients*, ϵ (at concentration, $C=$ 1 mM per liter, and at depth, $d=$ 1 cm.), against wave-length in mu, ϵ is a negative logarithmic function of the amount of light transmitted by the solution, much the same as pH is the negative log. of H^+, the hydrogen ion concentration, ϵ, not the light transmitted, is proportional to the concentration. Molar concentrations of reference for hemin derivatives refer to the weight containing one iron atom; in the case of hemoglobin the equivalent weight is 16,700, and 1 mM. per liter equals 16.7 Gm. per liter, or 1.67 Gm. per 100 ml. The millimolar concentration has proved convenient and unequivocal for the spectrophotometric notation of the various hemin derivatives.[38a] Since hemoglobin, hemin and hemochromogen derivatives may be converted respectively to spectroscopically practically identical cyan-methemoglobin,[38a] hemin dicyanide,[38b] and hemochromogen monocyanides,[38b] the cyanide derivatives were used for the quantitation of total hemin pigments in the various samples.

The comparison of the absorption spectrum data upon the peritoneal fluid and gut contents with known hemoglobin derivatives was materially aided by reliable information upon the latter, available from extensive work in the laboratory of one of us (DLD).

CLINICAL COURSE

Six of the seven animals responded in similar manner to the procedure and died between 28.25 and 48 hours after operation, with an average survival

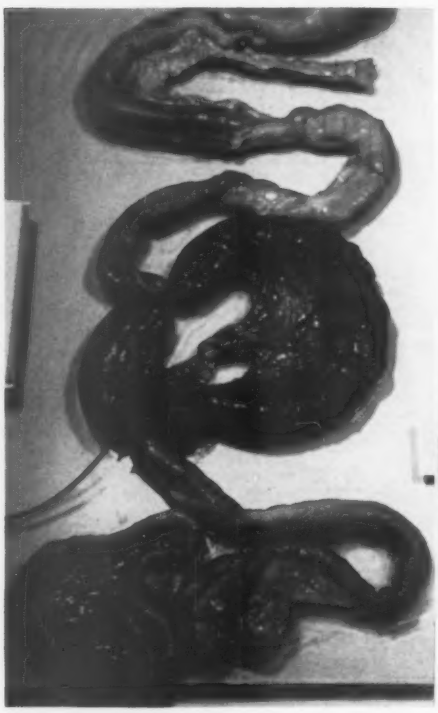


FIG. 2

FIG. 3

FIG. 2.—Photograph of the strangulated segment from dog. No. 365. This segment measured 75.0 cm. in length.

FIG. 3.—Photograph of the resected segment of bowel from dog No. 295. The strangulated segment measured only 25.0 cm. in length and was markedly thickened. The sharp line of demarcation is clearly shown.

time of 36 hours. This represents a definite prolongation of life, for in untreated animals with a similar length of strangulated gut death usually occurs between seven and 24 hours.[39-46] These dogs exhibited a black, necrotic, gangrenous, nonperforated, elongated, dilated[39, 40, 47-49] segment of gut. The loops were elongated some 25 to 50 per cent, and the wall was moderately to markedly thinned out (Fig. 1), but in no case had perforation occurred. There was an extremely sharp line of demarcation above and below the strangulated segment, and we found none of the changes in normal bowel described by Moon and Morgan.[41] One of these six animals (No. 365) demonstrated a

volvulus at autopsy, with a venous obstruction to the proximal obstructed bowel distal to the segment which had been purposely strangulated. The strangulated segment in this animal measured 75.0 cm. in length (Fig. 2). As there was no evidence of leakage at the proximal turned-in end nor at the entrance of the tube into the gut, this animal is included in the series and merely represents a more extensive strangulation.

The seventh animal (No. 295) lived for 75 hours, at which time resection of the strangulated segment was performed. The resected segment was blackish brown in color, extremely thickened, and measured only 25.0 cm. in length (Fig. 3).

The peritoneum in all cases revealed mild inflammatory changes and plastic exudate in the region of the loop, but in no case were necrotic areas present. The picture was never that of a bacterial peritonitis.

Postoperatively, the animals remained in relatively good condition, moving freely about in the cage up until one to four hours of death. At this time a striking change occurred. The animals obviously became sicker. Retching and vomiting, which had begun in all cases between eight and 14 hours, consisting of a foul smelling bloody fluid, became severe and constant. This final period was quite similar to that observed by Blain *et al.*[47] and Blain and Kennedy[48] in their dogs. Death occurred very suddenly and was preceded by convulsive movements of the extremities and gasping respirations. Femoral arterial pulsations were easily palpable in all cases up until several minutes of death, and the animal did not appear to be in clinical shock. Five of the six animals which died developed a terminal rise in the temperature to 103 to 107.6° F. just before death, and three of these were over 105° F.

It may be noted in Table II that the hematocrit and hemoglobin values were well maintained throughout the course of survival, only one animal (No. 347) showing a moderate fall. Large amounts of fluids were required to maintain the animals. The total fluid intake ranged between 3000 and 6700 cc. Administration of whole blood varied from 15.0 to 72.0 cc. per Kg. per 24 hours and of 5 per cent glucose in saline from 100 to 340 cc. per Kg. per 24 hours. The amount of peritoneal fluid removed over the course of survival varied from 603 to 1573 cc.

A study of the gut contents and peritoneal fluid revealed a constant sequence of events which was borne out by detailed chemical, bacteriologic, and spectrophotometric studies.

Within two to four hours after operation a small amount of reddish-black, odorless, coagulable fluid with a specific gravity between 1030 and 1040 and a hemoglobin content similar to that in the blood was aspirated from the strangulated gut lumen. The amount of this fluid entering the lumen was small at first but increased as the damage to the gut wall increased. At around 12 hours this fluid became black in color, noncoagulable, had a foul odor, and the specific gravity fell to between 1015 and 1024. From this point on the gross character of the fluid did not change, but the volume markedly increased. This later fluid in the gut lumen has been similarly described in strangulated

closed loops,[39, 42, 43, 45, 50] in simple strangulation obstruction[47, 48] and in isolated jejunal loops.[51]

On the other hand, the peritoneal fluid at two to four hours was pink or strawberry colored, clear, odorless, and had a specific gravity between 1019 and 1027. The physical properties as well as the chemical studies (Table III, Fig. 4) revealed that this fluid owed its character to the presence of blood and unchanged hemoglobin and, as shown by Laufman and Method,[52] apparently was derived early almost entirely from the serosal side of the strangulated gut. This continued to be the type of fluid recovered from the peritoneal

TABLE II.—*Intake and output data, hemoglobin and Hematocrit Readings on the Strangulated Animals*

Dog	Length of Survival in Hours	Fluid Change First Noted (Hour)	Intake					
			Blood		Glucose Saline		Gelatin	
			cc./L of S	cc./Kg./24h	cc./L of S	cc./Kg./24h	cc./L of S	cc./Kg./24h
331	42	36	1085	65	5525	340	100	6
237	48	48	660	24	2800	101	340	12
235	32	28	980	72	2425	182	200	15
357	35½	34	695	31	2275	101	100	5
347	30	29	805	38	2200	104	400	19
295	75*	..	550	15	4500	120	200	5
365	28¼	28	1000	50	2455	125	330	17

Output									
Peritoneal Fluid		Gut Contents		Urine and Vomitus		Hematocrit		Hemoglobin	
cc./L of S	cc./Kg./24h	cc./L of S	cc./Kg./24h	cc./L of S	cc./Kg./24h	Initial	Terminal	Initial	Terminal
1080	65	87	5	4040	245	55	57	20	19
603	22	53	2	2450	89	47	54	16	18
1400	106	38	3	1495	113	41	46	14	16
1098	48	47	2	1290	58	39	40	13	14
845	41	535	26	615	29	56	37	19	13
674	18	115	3	2425	65	45	43	15	15
1573	80	247	12	1380	70	52	49	18	16

* This animal never developed the fluid change, and the strangulated segment was resected at 75 hours.

cavity for a relatively long period of time. During the early stages this fluid was very abundant but decreased as the process progressed, possibly due to a thrombosis of the serosal vessels[52] or of the mesenteric veins proximal to the ligature.[22, 49] At variable stages, corresponding closely with the abrupt change in the clinical condition of the animal, the fluid recovered from the peritoneal cavity changed to a reddish black and later to a black fluid very similar in its physical and chemical characteristics to the bowel contents (Table III) (Fig. 4). The death of the animal occurred within one to four hours after the appearance of this fluid in the peritoneal cavity. The animal, which lived for 75 hours and was then reoperated upon, never developed the black fluid either in the gut or in the peritoneal cavity. Undoubtedly some degree of

TABLE III.—*Studies on the Nitrogenous Substances in the Blood, Peritoneal Fluid and Gut Contents*

(All values in mg/100 cc.)

Hours after Operation	DOG 331					237					235					357					347					295					365				
	UN	NPN	URIC ACID	CREAT-ININE	TN	UN	NPN	URIC ACID	CREAT-ININE	TN	UN	NPN	URIC ACID	CREAT-ININE	TN	UN	NPN	URIC ACID	CREAT-ININE	TN	UN	NPN	URIC ACID	CREAT-ININE	TN	UN	NPN	URIC ACID	CREAT-ININE	TN	UN	NPN	URIC ACID	CREAT-ININE	TN
CONTROL	16					16	31				13	31	0·51	1·2		49	67	0·73	2·09		27	52	0·89			23	44				20	66	0·94	1·89	
4	14																																	
8	19					25																												
12											13	24	0·70	0·65		27	43	0·56	1·56															
20	19					12					17	37	0·74	1·30		31	56	0·59	1·50															
24	16					14																												
28	24																													19	52	1·65	1·50	
29																														DIED, 28¼ HRS				
30	15																				50	71	0·86											
32																					61	78	0·79	2·61										
35½											19	43	1·53	2·08		41	62	0·66	1·63		DIED, 30 HRS												
36	19										DIED, 32 HRS					46	91	1·74	2·74															
42	22															DIED, 35½ HRS																		
44	DIED, 42 HRS					22	53																											
48						36	65																			23	44							
22						DIED, 48 HRS																				25	35								
																										RESECTED, 75 HRS								
2																					13	31	0·58	1·24	1170									
4	14																									16	20			630	11	24	0·49	0·72	1040
8	6					6	10																											
12											5	13	0·35			23	30	0·56	1·43	629														
20	5										10	19	0·51	1·32	596	26	32	0·59	1·30															
24	6					5	18			552																								
28	8				427																30	43	0·64	1·82	1220						13	29	0·91	1·50	1050
29																															FLUID CHANGE, 28 HRS			
30																					61	78	1·13	2·08	1230									
32	11										25	41	0·29	1·56	1080	31	43	0·59	1·63	546	FLUID CHANGE, 29 HRS												
35½											FLUID CHANGE, 28 HRS					60	68	0·31	2·48	461													
36	7				635	7	17			556						FLUID CHANGE, 34 HRS																		
42	16				794																													
44	FLUID CHANGE, 36 HRS																																	
48						56	105		2·02	692																11	23			500					
72						FLUID CHANGE, 48 HRS																				10	18			532					
																										NO FLUID CHANGE								
2																					13	61	2·76	1·82	2800									
4	12					7	37																			12	29			417	10	64	4·04	0·85	1370
12											37	64	0·19	0·78	2400	29	67			2330														
24						14	23																								36	59	0·19	0·85	1130
28																					169	190	0·34	2·08	599									
30											124	208	1·09	1·63	1850																			
32																128	185	0·73	2·48	707														
35½																																		
42	75																																	
44						20	27																											
48						86	270		3·19	865																28	30			185					
72																										21	21			128				

Blood	Peritoneal Fluid	Bowel Content

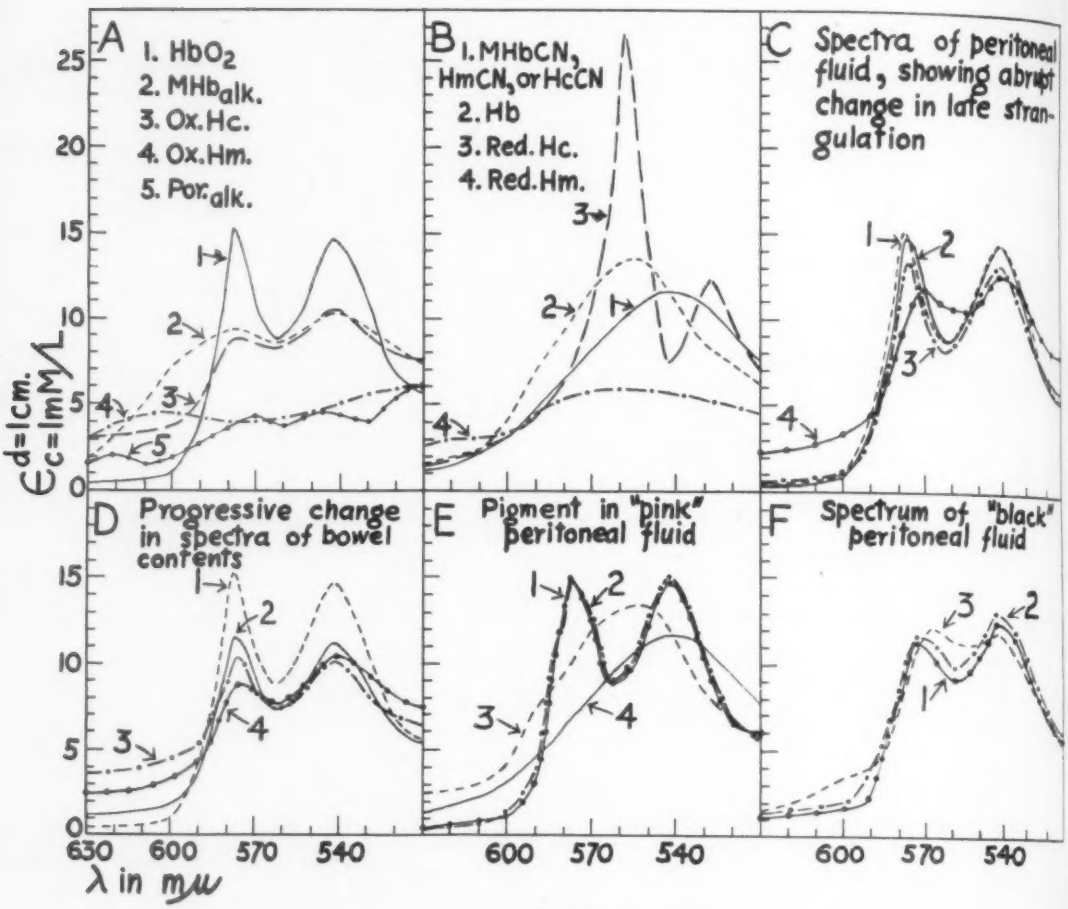


FIG. 4

FIG. 4.—Character and identification of absorption spectrum curves obtained from peritoneal fluid formed after the experimental intestinal strangulation (C, E, and F) and from the contents of the strangulated bowel segment (D). Absorption spectrum curves obtained from blood or derived from the hemoglobin of blood are presented for comparison (A and B).

A.—Curve 1, HbO_2, oxyhemoglobin;[59] Curve 2, $MHb_{alk.}$, alkaline methemoglobin, pH 9.15;[60] Curve 3, Ox. Hc., oxidized globin hemochromogen or globanferriprotoporphyrin;[61] Curve 4, Ox. Hm., oxidized hemin or ferrihemin;[61] Curve 5, $Por_{alk.}$, alkaline porphyrin.

B.—Curve 1, MHbCN, cyanmethemoglobin;[59] HmCN, hemin diacyanide;[62] or HcCN, monocyande derivative of oxidized globan ferriprotoporphyrin cyanide,[62, 63] derived respectively from 1 or 2 in A, 4 in A, and 3 in A; Curve 2, Hb, reduced or deoxygenated hemoglobin, derived from 1 or 2 in A by addition of hydrosulfite, $Na_2S_2O_4$; Curve 3, Red Hc. (reduced globin hemochromogen or globan ferroprotoporphyrin[61, 63] derived from 3 in A by addition of $Na_2S_2O_4$; Curve 4, Red. Hm. (reduced hemin or ferrohemin,[61] derived from 4 in A by addition of $Na_2S_2O_4$).

C.—Absorption spectrum curves of peritoneal fluid (from dog No. 357) removed at different times following establishment of strangulation obstruction. The curves illustrate the abrupt appearance (reflected in the abrupt change in color from "pink" to black) of the abnormal spectrum, Curve 4. Curve 1, unchanged oxyhemoglobin (same as 1 in A); Curve 2, at 4 hours, original total pigment concentration as MHbCN equals 0.649 Gm. per 100 ml.; Curve 3, at 32 hours, original total pigment concentration as MHbCN equals 0.387 Gm. per 100 ml; Curve 4, at 35 hours, original total pigment concentration as MHbCN equals 1.14 Gm. per 100 ml. (Legend continued on opposite page.)

revascularization occurred in the strangulated loop of this animal. Microscopically, the mucosal layer was intact whereas in the animals which died varying degrees of destruction were present.

CHEMISTRY

Blood. No significant change was noted in the chlorides, calcium[47, 48] or potassium.[53] The CO_2 combining power was moderately decreased.[47, 48] The amylase in the blood was decreased markedly within 12 to 24 hours following anesthesia and operation.[54] Eight hours after strangulation the serum lipase was 1.0 cc. or above in three of the six animals in which studies were made, and in one of the three it was also elevated at death. We have attached much accuracy to our determinations of serum lipase in the dog[55] and feel these elevations to be significant.

Peritoneal fluid. The protein content of the peritoneal fluid was in most instances between 3.4 and 4.5 Gm. per 100 cc.[45] The hematocrit of the early peritoneal fluid usually ranged from one up to less than six although in one animal (No. 347) values of 14 to 28 were obtained. No hematocrit readings could be obtained in the reddish black or black peritoneal fluid. The chloride content of the peritoneal fluid was slightly higher than that of the blood, and in two animals peritoneal fluid potassium levels were not elevated.[53] The amylase in the early peritoneal fluid varied directly with that of the blood.

Nitrogen studies in blood, peritoneal fluid and gut contents. We attach no significance to slight variations in the uric acid and creatinine which we obtained (Table III), and in no case did we find values for creatinine as high as those reported by Cooke, Rodenbaugh and Whipple.[56] In all the dogs which died, except the animal with the 75.0 cm. strangulation (No. 365), there was a slight to moderate increase in the blood urea nitrogen[39] and blood nonprotein nitrogen.[39, 45, 47, 48] The increase averaged 65 per cent for the blood urea nitrogen and 55 per cent for the nonprotein nitrogen. In the peritoneal fluid

---

D.—Absorption spectrum curves of contents of strangulated bowel segment (from dog No. 357), showing progressive change at an appreciably earlier time than in the peritoneal fluid (curves in C) toward fluid with the characteristic abnormal spectrum. Curve 1, unchanged oxyhemoglobin (same as 1 in A); curve 2, at 12 hours, original concentration of total pigment as MHbCN equals 0.81 Gm. per 100 ml.; Curve 3, at 27 hours, original concentration of total pigment as MHbCN equals 2.12 Gm. per 100 ml.; Curve 4, at 35 hours, original total pigment concentration as MHbCN equals 2.14 Gm. per 100 ml.

E.—Identification of spectrum of "pink" peritoneal fluid (from dog No. 235) as that of unchanged oxyhemoglobin. Curve 1, at 24 hours, original concentration of total pigments as MHbCN equals 0.432 Gm. per 100 ml., pH equals 8.0 (compare with curve 1 in A); Curve 2, obtained after addition of solid cyanide to solution yielding Curve 1 (no change); Curve 3, obtained after addition of solid $Na_2S_2O_4$ to solution yielding Curve 1 (compare with Curve 2 in B); Curve 4, obtained after addition of ferricyanide (for oxidation) and cyanide to solution yielding Curve 1 (compare with Curve 1 in B). Practically the same curve as 1 was obtained from a specimen removed at 28 hours.

F.—Abnormal behavior of pigment in "black" peritoneal fluid (from dog No. 235) towards addition of cyanide or $Na_2S_2O_4$. Curve 1, at 32 hours, original concentration of total pigment as MHbCN equals 4.46 Gm. per 100 ml., pH equals 9.2 (compare with Curve 4 in C and D); Curve 2, obtained after addition of solid cyanide to solution yielding Curve 1 (see the text); Curve 3, obtained after addition of solid $Na_2S_2O_4$ to solution yielding Curve 1 (see the text).

of the same group of animals the urea nitrogen showed an average increase of 362 per cent and the nonprotein nitrogen of 353 per cent. It will also be noted that this increase was not a gradual one but occurred suddenly during the late stages after the black fluid had appeared. The urea nitrogen and nonprotein nitrogen of the gut contents showed an average increase of 704 per cent and 309 per cent respectively. Here, also, it would seem that a late increase occurred (No. 237).

TABLE IV.—*Bacteriologic Studies on the Blood, Peritoneal Fluid and Gut Contents*

Dog No.	Peritoneal Fluid		Blood	Gut Contents
	Pink	Black or Red Black		
331	Hemo. clostridia B. coli Strep. viridans	Hemo. clostridia B. coli Non-hemo. strep.	Negative throughout	
237	Hemo. clostridia B. coli Salmonella Non-hemo. strep.	Hemo. clostridia B. coli Salmonella Non-hemo. clost. Non-hemo. strep.	36 h.—negative 48 h.—B. coli Non-hemo. clost.	
235	Hemo clostridia B. coli Hemo. strep. Non-hemo. strep.	Hemo. clostridia B. coli Hemo. strep. Non-hemo. strep. Non-hemo. clost.	Negative throughout	
357	Hemo. clostridia B. coli Hemo. strep. Non-hemo. strep. Non-hemo. clost. A. aerogenes	Hemo. clostridia B. coli Hemo. strep. Non-hemo. strep. Non-hemo. clost. A. aerogenes B. proteus	32 h.—Negative 34 h.—A. aerogenes 35 h.—Hemo. clostridia B. coli Hemo. strep. Non-hemo. strep. A. Aerogenes B. proteus	Hemo. clostridia B. coil Hemo. strep. Non-hemo. strep. Non-hemo. clost. A. aerogenes B. proteus
347	Hemo. clostridia B. coli Non-hemo. strep. Non-hemo. clost. A. aerogenes	Hemo. clostridia B. coli Hemo. strep. Non-hemo. strep. Non-hemo. clost. B. proteus	Negative throughout	Hemo. clostridia B. coli Non-hemo. strep. Non-hemo. clost. B. proteus
295	Hemo. clostridia B. coli Hemo. strep. Non-hemo. strep. Non-hemo. clost. Eberthella		Negative throughout	Hemo. clostridia B. coli Hemo. strep. Non-hemo. strep. Non-hemo. clost. Eberthella
365	Hemo. clostridia B. coli Hemo. strep. Non-hemo. strep. A. aerogenes	Hemo. clostridia B. coli Hemo. strep. A. aerogenes	Negative throughout	Hemo. clostridia B. coli Hemo. strep. Non-hemo. strep. Non-hemo. clost. A. aerogenes

Bacteriology. The peritoneal fluid has been found to be sterile at four to six hours[43, 57] and even as late as 19 to 20 hours.[47-49] In general, we found the peritoneal fluid to be sterile up until 14 to 20 hours, at which time the flora of the strangulated gut began to appear, and the late pink peritoneal fluid contained, qualitatively at least, almost identically the same organisms as found

in the red-black or black peritoneal fluid (Table IV). In three of the animals in which the gut contents were cultured just prior to death, the black fluid contained the same organisms as were found in the gut. It will be noted, however, that in these cases the same organisms were present in the pink fluid as early as 20 hours. In the animal which was resected at 75 hours the peritoneal fluid contained qualitatively the same organisms at 29 hours as were recovered from the resected segment at 75 hours. Hemolytic clostridia, *B. coli,* and nonhemolytic streptococcus were present in the peritoneal fluid in all cases.[58]

Positive blood cultures were obtained just before death in two animals. In both cases the black fluid was present in the peritoneal cavity at the time positive cultures were obtained.

Spectrophotometric findings. In Figure 4, A to F and its accompanying legend, typical results of the spectrophotometric measurements on the peritoneal fluid and bowel contents are presented together with an interpretation of the significance of the spectra. The latter is aided by a comparison with absorption spectrum curves obtained from normal hemolyzed blood or derived from the hemoglobin in blood by physical or chemical treatment (A and B, Fig. 4). The following points appear to be established unequivocally:

1. The absorption spectrum of samples of the pink or strawberry colored peritoneal fluid, withdrawn sometimes as late as 32 hours after strangulation, was essentially that of unaltered oxyhemoglobin (E, Fig. 4).

2. The absorption spectrum of the black peritoneal fluid was markedly and characteristically different from that of oxyhemoglobin and quite identical with the abnormal spectrum of the contents of the strangulated bowel segment. Detailed spectrophotometric evidence cannot be presented here, but the findings (in other experiments than those reported in Figure 4) lend themselves to the clear interpretation that the degree of alteration of the spectrum of peritoneal fluid from the character of Curve 2 towards Curve 4 in C depends on the proportion of two components in the mixture, namely, the relative amounts of pink peritoneal fluid and black bowel contents.

3. In contrast with the abrupt late change in spectroscopic character found in the peritoneal fluid, the alteration towards the abnormal spectrum in the bowel contents was early and progressive (D, Fig. 4).

4. It may be seen that the abnormal spectra of the bowel contents or of the late peritoneal fluid bear a superficial resemblance to either alkaline methemoglobin (Curve 2 in A), or still more closely to oxidized globin hemochromogen (Curve 3 in A). Both methemoglobin and oxidized hemochromogens should react with cyanide to yield the spectrum typified by cyanmethemoglobin (Curve 1 in B). An examination of the curves in F makes it clear that the abnormal spectrum of the black peritoneal fluid cannot be accounted for by the presence of appreciable amounts of methemoglobin or oxidized hemochromogens, for there was unexpectedly little change after the addition of cyanide (2F). After the addition of $Na_2S_2O_4$ (3F) if methemoglobin were present, a change toward 2B should have been found, or if typical hemo-

chromogens were present in appreciable amounts, a change toward the striking spectrum 3B should have been found.

The atypical behavior of the black peritoneal fluid towards cyanide and $Na_2S_2O_4$ suggests that we are dealing with an unusual pigment or pigments. It should be mentioned that most of the pigment in the black bowel contents and black peritoneal fluid were hemoglobin or hemin derivatives since they responded typically to the addition of ferricyanide plus cyanide.

5. To conserve space the spectrophotometric studies upon the blood have not been presented. These demonstrate unequivocally that the abnormal pigment appears in the blood but only very soon after or simultaneously with its appearance in the peritoneal fluid.

DISCUSSION

That shock through the local loss of fluid[45] may account for death in experimental long loop strangulations is amply demonstrated.[40, 42, 45, 46, 57, 64, 65] However, even with adequate treatment for shock, life is prolonged but little.[22, 47, 48] That penicillin when combined with treatment for shock, dehydration, and electrolyte imbalance may prolong life in strangulation obstruction has been shown also and would indicate that bacteria or their products probably play a role in the cause of death.[47, 48] Here again the protection afforded is limited, and the existence of some other lethal agent is further indicated by the series herein reported.

The lethal action of the contents of a strangulated loop of gut has been shown by many workers,[40, 42, 43, 50, 66, 67] but heretofore there has been no conclusive evidence for the absorption into the blood stream of the intraluminal contents, nor can it be stated that death would result even if such substances were absorbed.

The occlusion of the veins to a segment of bowel, as occurs in experimentally produced strangulation, precludes this route as a source of absorption. Lymphatic absorption has been incriminated by some investigators,[40, 43, 49] but others have failed to prolong life by obstructing the lymphatics.[67, 68] The likeliest source of absorption would appear to be from the peritoneal cavity.[44, 45, 68] However, in practically all instances reported, the peritoneal fluid removed from strangulated animals has proved to be nontoxic when injected into other animals,[42-46, 50, 57, 69] thus indicating that noxious agents from the lumen had not entered the peritoneal fluid, or else that the noxious agents were not present in sufficient amount to be lethal when injected into other animals.[67]

Our studies have revealed that late in the course of strangulation obstruction in animals intensively treated to avoid hemorrhage, shock, dehydration, and electrolyte imbalance, the bowel wall becomes permeable to its intraluminal contents, and this fluid then passes out into the peritoneal cavity and thence into the blood stream. We believe, as do others,[39, 40, 45, 49, 56, 64] that the pink peritoneal fluid is but a filtrate of the circulating blood. We also think that the development of the reddish-black or black fluid is due to a filtration of

the strangulated gut contents through the devitalized bowel wall into the peritoneal cavity. Even after the complete occlusion of the venous channels, evidence of permeability of the gut wall to its intraluminal fluid occurred in none of our animals before 28 hours. This is longer than the length of survival of animals in which shock, dehydration and electrolyte balance have not been combatted.

That this black fluid is a "diluted" counterpart of the gut contents is also shown and would be expected in view of the continued outpouring of the pink or plasmalike fluid from the peritoneal surfaces in the presence of a devitalized segment of intestine within the peritoneal cavity.[57]

The death of the animal followed shortly after the development of the reddish-black or black fluid in the peritoneal cavity. In view of this fact and the known marked toxicity of the lumen contents, it would appear that some lethal factor was present in this later fluid. It is unlikely that the living bacteria or their end products are directly concerned with the death of the animal.[43, 57] While it is true that the black fluid contained, qualitatively, the same organisms as did the lumen contents just before death, it must also be remembered that these same organisms were present in the pink fluid from around 16 to 20 hours onward, yet death did not occur until a short time after the development of the black peritoneal fluid. The important role of the organisms indirectly by their action on the devitalized mucosa, however, has been indicated by Sarnoff and Fine[22] and Blain, *et al.*,[47, 48] and it is likely that the prolongation of life in the penicillin treated group of animals reported by Blain *et al.*[47, 48] was due to the fact that the destructive action of the organisms on the bowel wall was delayed, thereby lengthening the time in which the gut became permeable to its intraluminal contents.

If it is true that a noxious agent formed in the gut and absorbed into the blood stream is the cause of death in these animals, then much clarification of the route of absorption is afforded by our studies. Although the characteristic luminal contents were present within the lumen as early as 12 hours, death did not occur until soon after the reddish-black or black fluid had appeared in the peritoneal cavity, and in no case were we able to demonstrate spectrophotometrically the hemin or hemoglobin derivative in the blood stream until after it had appeared in the peritoneal cavity. The absorption from the lymphatics of the strangulated gut would, therefore, appear to be negligible.

While the characteristic absorption spectrum curve typifying black bowel contents and black peritoneal fluid has been defined, the identity of the pigment or pigments responsible for the abnormal spectrum has not been established. It remains for future investigation to establish whether the curve represents hemoglobin derivatives not hitherto described and originating from the blood pigment under the abnormal conditions in the strangulated bowel segment, or whether the spectrum is that of a mixture of common hemoglobin derivatives with less usual ones. Among the latter may be mentioned sulfhemoglobin[59] and porphyrins,[70] both of which types of pigments could conceivably

be formed in the intestine from hemoglobin. At present we have no evidence that either of such pigments is involved.

It is important to state clearly that at this stage we have no evidence whatever directly implicating the abnormal pigment or pigments with responsibility for the toxicity. Such close hemoglobin derivatives as methemoglobin are essentially nontoxic,[71] and at present there is little evidence that other derivatives or relatives of hemoglobin may be toxic, with the possible exception of porphyrins. It is sufficient to state that the pigments responsible for the abnormal spectrum are contained in the black peritoneal fluid, characterize it, and give evidence for its intestinal origin.

SUMMARY AND CONCLUSIONS

1. Late in the course of strangulation obstruction the bowel wall becomes permeable to its intraluminal contents, and this characteristically colored fluid passes out into the peritoneal cavity and is then absorbed into the blood stream. The death of the animal occurs soon after the appearance of this late black or reddish-black fluid in the peritoneal cavity.

2. By spectrophotometric analysis we have demonstrated that the character of the intraluminal contents is due in part to the presence of a hemin or hemoglobin derivative hitherto unreported *in vivo*, and by this method we have directly followed its passage from the gut lumen into the peritoneal cavity and from thence into the blood stream.

3. In view of the close correlation between the appearance of the black peritoneal fluid and the demise of the animal, it would appear likely that a lethal agent was present in this late fluid. If this is the true explanation, the "toxicity" of this fluid should be demonstrable on injection into recipient animals, and the subsequent report is concerned with this phase of the problem.

BIBLIOGRAPHY

[1] Fitz, R. H.: The Diagnosis and Medical Treatment of Acute Intestinal Obstruction. Boston Med. & Surg. J., **119**: 445–499, 469–472, 493–495, 523–528, 1888.

[2] Gibson, C. L.: A Study of One Thousand Operations for Acute Intestinal Obstruction and Gangrenous Hernia. Ann. Surg., **32**: 486–514, 1900.

[3] Scudder, C. L.: The Principles Underlying the Treatment of Acute Intestinal Obstruction: A Study of One Hundred and Twenty-one Cases of Acute Intestinal Obstruction from the Massachusetts General Hospital Clinic. Boston Med. & Surg. J., **159**: 491–497, 1908.

[4] Richardson, E. P.: Acute Intestinal Obstruction: A Study of a Second Series of Cases from the Massachusetts General Hospital. Boston Med. & Surg. J., **183**: 288, 1920.

[5] Finney, J. M. T.: Acute Intestinal Obstruction. Surg., Gynec. & Obst., **32**: 402–408, 1921.

[6] van Beuren, F. T., Jr., and B. C. Smith: Status of Enterostomy in Treatment of Acute Ileus: A Statistical Inquiry. Arch. Surg., **15**: 288–297, 1927.

[7] North, J. P.: Acute Intestinal Obstruction. Internat. Clin., **3**: 206–215, 1929.

[8] Taylor, W., W. S. Handley and D. P. D. Wilkie: Acute Intestinal Obstruction (Proc. Sec. Annual Meet., Bath) H. S. Souttar (General Discussion). British Med. J., **2**: 993–1004, 1925.

[9] Brill, S.: The Mortality of Intestinal Obstruction: Analysis of 124 Cases Operated upon at the Hospital of the University of Pennsylvania. Ann. Surg., **89**: 541–548, 1929.

[10] McIver, M. A.: Acute Intestinal Obstruction. I. General Considerations. Arch. Surg., **25**: 1098–1105, 1932.

[11] Miller, C. J.: A Study of Three Hundred Forty-three Surgical Cases of Intestinal Obstruction. Ann. Surg., **89**: 91–107, 1929.

[12] Christopher, F., and W. K. Jennings: Operative Mortality in Intestinal Obstruction. Ann. Surg., **99**: 332–337, 1934.

[13] Scudder, J., R. L. Zwemer and A. O. Whipple: Acute Intestinal Obstruction: Evaluation of Results in Twenty-one Hundred Fifty Cases; with Detailed Studies of Twenty-five Showing Potassium as a Toxic Factor. Ann. Surg., **107**: 161–197, 1938.

[14] Wangensteen, O. H.: Acute Bowel Obstruction: Its Recognition and Management. New England J. Med., **219**: 340–348, 1938.

[15] Johnston, C. G.: Decompression in the Treatment of Intestinal Obstruction. Surg., Gynec. & Obst., **70**: 365–369, 1940.

[16] McKittrick, L. S., and S. P. Sarris: Acute Mechanical Obstruction of the Small Bowel: Its Diagnosis and Treatment. New England J. Med., **222**: 611–622, 1940.

[17] Schlicke, C. P., J. A. Bargen and C. F. Dixon: The Management of Intestinal Obstruction. An Evaluation of Conservative Therapy. J. A. M. A., **115**: 1411–1416, 1940.

[18] Dennis, C., and S. P. Brown: Treatment of Small Bowel Obstruction. Procedure Used at the University of Minnesota Hospital. Surgery, **13**: 94–106, 1943.

[19] Eliason, E. L., and R. F. Welty: A Ten Year Survey of Intestinal Obstruction. Ann. Surg., **125**: 57–65, 1947.

[20] Calihan, R. J., J. D. Kennedy and A. Blain, III: Intestinal Obstruction: Study of 204 Acute Cases with Reference to Possible Efficacy of Anti-bacterial Therapy. Bull. Johns Hopkins Hosp., **79**: 21, 1946.

[21] Moses, W. R.: Acute Obstruction of the Small Intestine. A Report of One Hundred and Eighteen Cases. New England J. Med., **234**: 78, 1946.

[22] Sarnoff, S. J., and J. Fine: The Effect of Chemotherapy on the Ileum Subjected to Vascular Injury. Ann. Surg., **121**: 74, 1945.

[23] Barbour, H. G., and W. F. Hamilton: The Falling Drop Method for Determining Specific Gravity. J. Biol. Chem., **69**: 625, 1926.

[24] Kingsley, G. R.: The Determination of Serum Total Protein, Albumin, and Globulin by the Bieuret Reaction. J. Biol. Chem., **131**: 197, 1939.

[25] Karr, W. G.: A Method for the Determination of Blood Urea Nitrogen. J. Lab. & Clin. Med., **9**: 329, 1924.

[26] Folin, O., and N. Wu: A System of Blood Analysis. J. Biol. Chem., **38**: 81, 1919.

[27] Folin, O.: Standardized Methods for the Determination of Uric Acid in Unlaked Blood and in Urine. J. Biol. Chem., **101**: 111, 1933.

[28] ————: The Preparation of Sodium Tungstate Free from Molybdate, Together with a Simplified Process for the Preparation of a Correct Uric Acid Reagent (and Some Comments). J. Biol. Chem., **106**: 311, 1934.

[29] Peters, J. P., and D. D. Van Slyke: Quantitative Clinical Chemistry, p 516–537, 1932, Baltimore. Williams & Wilkins Company.

[30] Frame, E. G., J. A. Russell and A. E. Wilhelmi: The Colorimetric Estimation of Amino Nitrogen in Blood. J. Biol. Chem., **149**: 255, 1943.

[31] Somogyi, M.: Micromethods for the Estimation of Diastase. J. Biol. Chem., **125**: 399, 1938.

[32] Cherry, I. S., and L. A. Crandel, Jr.: The Specificity of Pancreatic Lipase: Its Appearance in the Blood After Pancreatic Injury. Am. J. Physiology, **100**: 266, 1932.

[33] Wilson, D. W., and E. G. Ball: A Study of the Estimation of Chloride in Blood and Serum. J. Biol. Chem., **79**: 221, 1928.

[34] Clark, E. P., and J. B. Collip: A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification. J. Biol. Chem., **63**: 461, 1925.

[35] Van Slyke, D. D., and G. E. Cullen: Studies of Acidosis. I. The Bicarbonate Concentration of the Blood Plasma; Its Significance and Its Determination as a Measure of Acidosis. J. Biol. Chem., **30**: 289, 1917.

[36] Dole, M.: Principles of Experimental and Theoretical Electro-Chemistry, pp. 427–435, 1935. McGraw-Hill International Clinic Series.

[37] Lenning, M. C.: The Use of the Flame Photometer in Biological Determination. In preparation.

[38] Photometry and Spectrophotometry, by Drabkin, D. L.: Chapter in Medical Physics edited by O. Glasser, 1944, Chicago. The Year Book Publishers, Inc., p. 967–1008.

[38a] Drabkin, D. L., and J. H. Austin: Spectrophotometric Studies: II. Preparation from Washed Blood Cells; Nitric Oxide Hemoglobin and Sulfhemoglobin. J. Biol. Chem., **112**: 51, 1935.

[38b] Drabkin, D. L.: Spectrophotometric Studies: IX. The Reaction of Cyanide with Nitrogenous Derivatives of Ferriprotoporphyrin. J. Biol. Chem., **142**: 855, 1942.

[39] Foster, W. C., and R. W. Hausler: Studies on Acute Intestinal Obstruction; Acute Strangulation. Arch. Int. Med., **34**: 697, 1924.

[40] Holt, R. L.: The Pathology of Acute Strangulation of the Intestine. British J. Surg., **21**: 582, 1934.

[41] Moon, V. H., and D. R. Morgan: Shock: The Mechanism of Death Following Intestinal Obstruction. Arch. Surg., **32**: 776, 1936.

[42] McIver, M. A., J. C. White and G. M. Lawson: The Role of the Bacillus Welchii in Acute Intestinal Obstruction, with Ligation of the Veins to the Obstructed Loop. Ann. Surg., **89**: 647, 1929.

[43] Murphy, F. T., and B. Vincent: An Experimental Study of the Cause of Death in Acute Intestinal Obstruction. Boston Med. & Surg. J., **165**: 684, 1911.

[44] Wahren, H.: The Intoxication in Intestinal Strangulation: An Experimental Study. Acta chir. Scandinav., **78**: 121, 1936.

[45] Evans, E. I.: The Mechanism of Shock in Intestinal Strangulation: An Experimental Study. Ann. Surg., **117**: 28, 1943.

[46] Maycock, W. d'A.: Intestinal Strangulation; The Depressor Properties of the Peritoneal Transudate in Intestinal Strangulation. British J. Surg., **25**: 677, 1938.

[47] Blain, A., III, J. D. Kennedy, R. J. Calihan and H. N. Harkins: Effect of Penicillin in Experimental Intestinal Obstruction: Cure of Strangulated Ileal Obstructions Treated with Penicillin Prior to Late Resections. Arch. Surg., **53**: 378, 1946.

[48] Blain, A., III, and J. D. Kennedy: Effect of Penicillin in Experimental Intestinal Obstructions; Studies on Strangulated Low Ileal Obstructions. Bull. Johns Hopkins Hosp., **79**: 1, 1946.

[49] Knight, G. C., and D. Slome: Intestinal Strangulation. British J. Surg., **23**: 820, 1936.

[50] Brooks, B., H. W. Schumacher and J. D. Wattenberg: Intestinal Obstruction; An Experimental Study. Ann. Surg., **67**: 210, 1918.

[51] Harper, W. H., and A. Blain, III: The Effect of Penicillin in Experimental Intestinal Obstruction. Bull. Johns Hopkins Hosp., **76**: 221, 1945.

[52] Laufman, H., and H. Method: The Role of Vascular Spasm in Recovery of Strangulated Intestine; Experimental Study. Surg., Gynec. & Obst., **84**: 675, 1947.

[53] Jorgenson, M. N., N. Dietz and F. C. Hill: Potassium as a Toxic Factor in Intestinal Obstruction. Proc. Soc. Exper. Biol. & Med., **43**: 282, 1940.

[54] Nemir, P., Jr., and B. L. Lecrone: Depression of Serum Amylase Following Sodium Pentobarbital Anesthesia. To be published.

55 Nemir, P., Jr., H. R. Hawthorne and B. L. Lecrone: Elevations of Serum Lipase in Experimentally Induced Appendiceal Peritonitis. Arch. Surg. In Press.

56 Cooke, J. V., F. H. Rodenbaugh and G. H. Whipple: Intestinal Obstruction. VI. A Study of Non-coagulable Nitrogen of the Blood. J. Exper. Med., **23**: 717, 1916.

57 Scott, H. G.: Intestinal Obstruction; Experimental Evidence on Loss of Blood in Intestinal Strangulation. Arch. Surg., **36**: 816, 1938.

58 Meleney, F. L., J. Olipp, H. D. Harvey and H. Z. Jern: Peritonitis: Synergism of Bacteria Commonly Sound in Peritoneal Exudates. Arch. Surg., **25**: 709, 1932.

59 Drabkin, D. L., and J. H. Austin: Spectrophotometric Studies: II. Preparation from Washed Blood Cells; Nitric Oxide Hemoglobin and Sulfhemoglobin. J. Biol. Chem., **112**: 51, 1935.

60 Austin, J. H., and D. L. Drabkin: Spectrophotometric Studies: III. Methemoglobin. J. Biol. Chem., **112**: 67, 1935.

61 Drabkin, D. L., and J. H. Austin: Spectrophotometric Studies: IV. Hemochromogens. J. Biol. Chem., **112**: 89, 1935.

62 Drabkin, D. L.: Spectrophotometric Studies: IX. The Reaction of Cyanide with Nitrogenous Derivatives of Ferriprotoporphyrin. J. Biol. Chem., **142**: 855, 1942.

63 Drabkin, D. L.: Spectrophotometric Studies: X. Structural Interpretation of the Spectra of Cyanide, Pyridine and Carbon Monoxide Derivatives of Cytochrome C and Hemoglobin. J. Biol. Chem., **146**: 605, 1942.

64 Gendel, S., and J. Fine: The Effect of Acute Intestinal Obstruction on the Blood and Plasma Volumes. Ann. Surg., **110**: 25, 1939.

65 Aird, I.: Experiments in Intestinal Obstruction; Role Played by Diminution of Effective Circulating Blood Volume in Acute Intestinal Obstruction. Edinburgh M. J., **44**: 28, 1937.

66 Gatch, W. D., H. M. Trusler and K. D. Avers: Effects of Gaseous Distention on Obstructed Bowel; Incarceration of Intestine by Gas Traps. Arch. Surg., **14**: 1215, 1927.

67 Wilkie, D. P. D.: Experimental Observations on the Cause of Death in Acute Intestinal Obstruction. British M. J., **2**: 1064, 1913.

68 Sperling, L.: Mechanics of Simple Intestinal Obstruction; An Experimental Study. Arch. Surg., **36**: 778, 1938.

69 von Albeck, V.: Aus gefuhrt am Universitatslaboratorium fur Medicinische Bacteriologie in Kopenhagen. Arch. fur Klin. Chir., **65**: 567, 1902.

70 Watson, C. J., and E. A. Larson: The Urinary Coproporphyrins in Health and Disease. Physiol. Rev., **27**: 478, 1947.

71 Drabkin, D. L.: Spectrophotometric Studies in Metabolism and Molecular Structure of Hemoglobin Derivatives. Proc. Fifth Summer Conference on Spectroscopy and Its Applications, 1937, John Wiley & Sons, Inc., N. Y., p. 94, 1938.

THE CAUSE OF DEATH IN STRANGULATION OBSTRUCTION: AN EXPERIMENTAL STUDY

II. LETHAL ACTION OF THE PERITONEAL FLUID*

PAUL NEMIR, JR., M.D., H. R. HAWTHORNE, M.D., ISIDORE COHN, JR., M.D., AND DAVID L. DRABKIN, M.D.

PHILADELPHIA, PA.

FROM THE HARRISON DEPARTMENT OF SURGICAL RESEARCH, SCHOOL OF MEDICINE, AND THE DEPARTMENTS OF SURGERY AND PHYSIOLOGICAL CHEMISTRY, GRADUATE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA

IN OUR FIRST COMMUNICATION[1] we showed that, late in the course of strangulation obstruction in dogs intensively treated for shock, dehydration, and electrolyte imbalance, the peritoneal fluid changed from a pink, odorless, coagulable fluid to a reddish-black or black, malodorous, non-coagulable fluid. In view of the rapid demise of the animal after the appearance of the black fluid in the peritoneal cavity and its rapid absorption into the blood stream, it seemed likely that some lethal factor was present in this fluid. This report is concerned with the injection of the peritoneal fluid, removed from the strangulated animals at various intervals, into normal animals by both intravenous and intraperitoneal routes.

METHOD

Normal, unanesthetized dogs were used as recipient animals. In no case was the circulating blood volume decreased[2] before injection. The total amounts of fluid were in all cases delivered intraperitoneally between two and eight hours. Intravenous injections were given either by rapid drip into a leg vein if the amount was large, or slowly by syringe injection if the amount was small. Following injection, the animals were carefully observed, and the temperatures were followed in a number of the dogs. Peritoneal fluids were kept in the ice box at all times between sample collection and administration and warmed to room temperature just before administration. The fluid was, in all cases, injected unchanged within a few hours after collection. In those animals which appeared to be moribund, blood was taken for culture and for spectrophotometric analysis. All animals, except No. 11, were posted immediately after death.

RESULTS AND DISCUSSION

The injection of peritoneal fluid or gut contents from animals having a strangulation obstruction into normal animals has been used by many investigators as a method of determining the toxicity of these substances. While

* Aided by a grant from the National Drug Company, Philadelphia, Pennsylvania. We are deeply indebted to M. W. Allam, V.M.D.; to B. L. Lecrone, M.S.; and to Miss A. C. Nichols for their invaluable assistance. Our thanks are also due to E. A. Case, M.D., who kindly reviewed the microscopic sections. Submitted for publication April, 1949.

the criteria for "toxicity" have varied,[3-5] the peritoneal fluid, almost uniformly, has been shown to have essentially no effect on the recipient,[2, 6-12] even when injected in amounts up to 200 cc.;[4] and the late gut contents have been shown almost invariably to cause death in such small amounts as several cc.s.[8, 9, 13, 14] It is of interest to note, however, that Foster and Hausler[10] injected 80 to 100 cc. of loop fluid, filtered through sterile gauze only, from strangulated dogs dying between 7 and 12 hours, intraperitoneally into recipient animals without causing death.

In this study the criterion for toxicity of the peritoneal fluid was the death of the animal. Although occasional vomiting and diarrhea followed the injection of very large amounts of pink fluid, if death did not ensue the injection was recorded as having "no effect." Obviously, the amount of fluid to be injected was, as in the past, purely arbitrary. However, we feel that much clarification of this point may be gained by (1) a comparison of the total amounts of pink fluid and red-black or black fluid injected, and (2) our spectrophotometric studies.

A review of Table I reveals the following: The pink, odorless, coagulable peritoneal fluid which was present up until several hours before death in the strangulated animals did not cause the death of the recipient in any of six animals injected either intraperitoneally or intravenously in amounts up to 40 to 50 cc. per Kg. of body weight. We have injected intravenously as much as 425 cc. of this fluid into an animal over a period of one hour without any effects except a mild transient vomiting. In many cases this pink peritoneal fluid was withdrawn as late as 24 to 28 hours after strangulation.

It is of interest that the bacterial flora of this pink fluid was practically identical with the reddish-black, or black, fluid qualitatively and death was not caused by injection of the bacteria.[8, 11]

The animals which received the reddish-black or black fluid behaved in a different manner. Four of the seven animals so injected died, two at six and seven hours after intraperitoneal injection, and the remaining two at five hours and 30 to 40 hours after intravenous injection. Another animal (No. 13) died five days after receiving red-black fluid intravenously. It was thought that the death of this animal was due, at least in part, to distemper, and it is therefore not considered as one of the animals dying from the injection. It is true that large amounts (35 cc. per kilo.) of the black fluid were given intraperitoneally, but even these amounts were considerably less than the pink fluid given either intraperitoneally or intravenously. Of the two dogs that died following intravenous administration, it will be noted that one died five hours after receiving only 24 cc., and the other died between 30 to 40 hours after receiving 100 cc.

The reactions of the animals which died were similar in all cases whether the fluid was given intravenously or intraperitoneally. Up until around two hours after injection the animals appeared normal. After this period, however, their condition rapidly deteriorated, vomiting became more frequent and severe, and the animals were usually moribund several hours before death.

TABLE I.—*Lethal Action of the Peritoneal Fluid*

Recipient Animal	Weight (kg.)	Peritoneal Fluid Injected: Source	Hrs. Between Strangulation and Withdrawal	Character of Fluid	Organisms Present	Amount—Total Cc.	Amount—Cc./Kg.	Method	Interval of hrs. Given	Comment
1	9.0	331	3½–24	Pink, odorless, coagulable	Hemo. clostridia	400	45	I.P.	8	No effect
2	2.0	232	12–28	Pink, odorless, coagulable	Hemo. clostridia B. coli Salmonella	350	50	I.P.	4	No effect
3	7.0	357	24 or less	Pink, odorless, coagulable	B. Coli Hemo. strep.	280	40	I.P.	2	No effect
4	7.0	347	24 or less	Pink, odorless, coagulable	Hemo. clostridia B. coli Non-hemo. strep. Non-hemo. clost. A. aerogenes	210	30	I.V.	2½	No effect
5	6.7	295	24 or less	Pink, odorless, coagulable	B. coli Hemo. strep. Non-hemo. strep.	300	45	I.V.	3	No effect
6	8.5	365	20–25	Pink, odorless, coagulable	Hemo. clostridia B. coli Hemo. strep. Non-hemo. strep. A. aerogenes	425	50	I.V.	1	No effect
7	9.0	331	28–32	Pink, odorless, coag.	Hemo. clostridia 100					
			36	Reddish-black	B. coli 100	360	40	I.P.	3	No effect
			42	Black, foul, non-coag.	Strep. vividans 160					
8	10.0	235	28–32	Black, foul, non-coagulable	Hemo. clostridia B. coli Hemo. strep. Non-hemo. strep. Non-hemo. clost.	350	35	I.P.	1¼	Died 6 hrs
9	10.0	357	35	Black, foul, non-coagulable	Hemo. clostridia B. coli Hemo. Strep. Non-hemo. strep.	350	35	I.P.	6	Died 7 hrs.
10	7.3	357	35	Black, foul, non-coagulable	Non-hemo. clost. A. aerogenes B. proteus	24	3	I.V.	At once	Died 5 hrs. T = 107[1]
11	5.5	347	29 30	Red-black, non-coag. Black, foul, non-coag.	Hemo. clostridia Hemo. strep. Non-hemo. strep. 35 Non-hemo. clost. 65 A. Aerogenes B proteus	100	18	I.V.	2	Died 30–40 hrs. T = 104[6] at 4½ hrs.
12	8.0	365	28¼	Red-black, faint odor, non-coag.	Hemo. clostridia B. coli	155	19	I.V.	2	No effect
13	8.3	365	28	Red-black, faint odor, non-coag.	Hemo. strep. A. aerogenes	125	15	I.V.	1	Died 5 days—distemper T = 105[2] at 4½ hrs.

The animal which lived for 30 to 40 hours was listless and obviously sick during this entire period. No temperatures were taken in the animals receiving the intraperitoneal injections, but it will be noted that the temperature was 107.2° F. just before death in one of the animals receiving an intravenous injection, and 104.6° F. at approximately the same time after injection in the other. This is interesting in view of the high temperature elevation observed terminally in the strangulated animals.[1] Blood cultures drawn 4.5 to 6.5 hours after the injection into the recipient animals which died were negative on direct inoculation onto blood agar in three cases, and positive for *B. Coli* in the remaining case.

The necropsy findings in the two animals which died following intraperitoneal injection were identical and limited to the abdomen. The peritoneum was mildly injected in areas. The peritoneal cavities contained 150 cc. (No. 8) and 275 cc. (No. 9) respectively, of a red-brown fluid somewhat similar to that injected. In both cases there was an intense injection of the mesentery, especially marked as the mesentery approached the bowel. The duodenal mucosa, and the jejunal and ileal mucosa to less extent, showed submucosal hemorrhages. Aside from a moderate congestion of all the abdominal viscera, no other pathologic findings were noted. No gross abnormalities were noted at necropsy in the animals receiving the intravenous injection.

While our overall results with injections of the peritoneal fluid clearly indicated the great toxicity of the black peritoneal fluid, nonetheless, there appeared to be marked variations in the toxicity of this fluid from different animals. Variations in the character of the black or red-black fluid, as suggested clinically by the different responses, was objectively confirmed by our spectrophotometric studies, and the cause for this variation was conceivably explained by a review of the intake and output data for the strangulated animals. The peritoneal fluid from dog No. 357 was lethal when only 24 cc. was injected intravenously. This peritoneal fluid gave a spectrophotometric curve (Curve 3, Fig. 1) very similar to the one given by the bowel contents from this animal, and would be expected since approximately 500 cc. of intraluminal contents passed into the peritoneal cavity in the last few hours of survival. The fluid from dog No. 347 was lethal to the recipient at 30 to 40 hours after 100 cc. intravenously and the change toward the characteristic abnormal spectrum was less marked. As we were completely aspirating the strangulated lumen in this animal, less fluid passed out into the peritoneal cavity, and therefore, the dilution factor by the pink fluid was greater. Direct evidence of this was obtained from the values for original concentration of total pigments as cyan-methemoglobin. The peritoneal fluid of dog No. 365 (no death in recipients with 155 and 125 cc. respectively intravenously) showed the least marked spectrophotometric changes (Curve 4, Fig. 1), and here again, the dilution factor was of considerable magnitude.

The degree of toxicity, as expected, was greater in those animals in which a greater amount of the lumen contents diffused through the wall into the peritoneal cavity. This is borne out by the fact that the gut lumen was almost

devoid of fluid at post mortem in two animals having highly toxic fluids (No. 235 and 357, Curves 2, 3, Fig. 1), whereas almost 600 cc. of peritoneal fluid in each was present despite the fact that the peritoneal cavity was evacuated as completely as possible less than four hours before death. Animal No. 347 developed almost 300 cc. of black peritoneal fluid despite the fact that 200 cc. of gut contents was removed one hour prior to death, and the peritoneal fluid from this animal was also lethal.

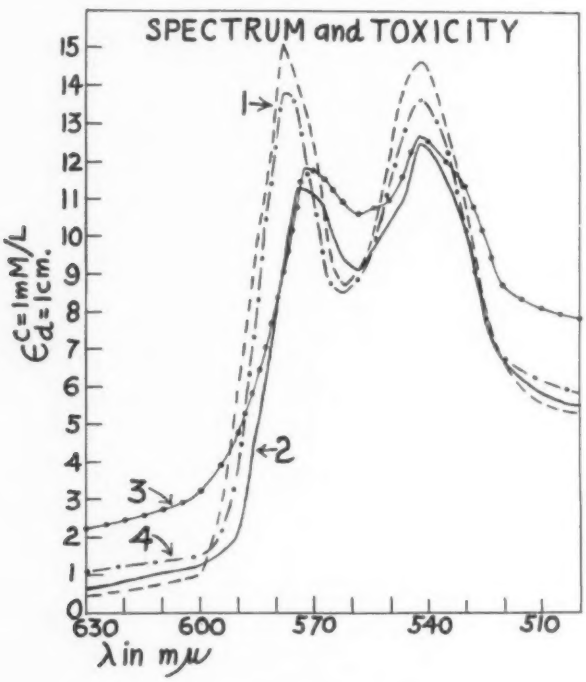


FIG. 1.—Data illustrating the relationship of toxicity to degree of spectral abnormality in comparison with normal oxyhemoglobin spectrum.

Curve 1. Absorption spectrum curve of unchanged oxyhemoglobin.

Curve 2. Absorption spectrum curve of peritoneal fluid (highly toxic) collected at 32 hours after strangulation from dog No. 235. Original concentration of total pigment as cyan-methemoglobin was 4.46 Gm. per 100 ml.

Curve 3. Absorption spectrum curve of peritoneal fluid (highly toxic) collected at 35 hours from dog No. 357. Original concentration of total pigment as cyan-methemoglobin was 1.14 Gm. per 100 ml.

Curve 4. Absorption spectrum curve of peritoneal fluid (relatively nontoxic), collected at 28 hours from dog No. 365. Original concentration of total pigment as cyan-methemoglobin was 3.24 Gm. per 100 ml.

We have stated[1] that the demonstration of an abnormal pigment, present first in the strangulated lumen, later in the peritoneal fluid, and finally in the blood, has been a useful method of following the course of events in the

strangulated animals. From the results herein reported, this finding assumes greater significance. It would appear that some relationship exists between the content of unidentified pigments responsible for the abnormal spectrum of the black peritoneal fluid and its toxicity. Some relationship is also indicated by the fact that one of the six animals which died following strangulation had only 40 cc. of black fluid in the peritoneal cavity at death and this fluid showed the most marked changes spectrophotometrically of any obtained. Also, it will be remembered that the altered curves were not obtained in the gut contents until around 12 hours. In view of the fact that Foster and Hausler[10] injected large amounts of less than 12 hour loop fluid into other animals intraperitoneally without causing death, a relation between the altered pigment and the toxicity of the fluid seems indicated.

CONCLUSIONS

1. The pink or strawberry colored peritoneal fluid, removed from animals with a strangulation obstruction, which owes its character to the presence of blood and unchanged hemoglobin, is non-toxic on injection into normal, recipient animals either by the intraperitoneal or intravenous routes even when rapidly administered in amounts up to 50 cc. per Kg. of body weight.

2. The late or black peritoneal fluid, which has been shown to be derived at least in part from the lumen of the strangulated gut is lethal on injection into normal, recipient animals by either the intraperitoneal or intravenous routes when administered in much smaller amounts than the pink fluid.

3. The toxicity of the peritoneal fluid samples removed in experimental strangulation obstruction bears a relationship of proportionality to its content of unidentified pigments responsible for the abnormal spectrum of the black peritoneal fluid.

4. It must be stressed that while the abnormal spectrum characterizes the toxic fluid, and, indeed, has served as a measure of the degree of toxicity of the fluid on injection into other animals, no evidence is at present at hand to identify the pigment itself as the toxic agent.

BIBLIOGRAPHY

[1] Nemir, P., Jr., H. R. Hawthorne, I. Cohn, Jr., and David L. Drabkin: The Cause of Death in Strangulation Obstruction; An Experimental Study. I. Clinical Course, Chemical, Bacteriologic and Spectrophotometric Studies. Ann. Surg., **130:** Nov., 1949. (Discussion preceding.)

[2] Maycock, W. d'A.: Intestinal Strangulation; The Depressor Properties of the Peritoneal Transudate in Intestinal Strangulation. British J. Surg., **25:** 677, 1938.

[3] Knight, G. C., and D. Slome: Intestinal Strangulation. British J. Surg., **23:** 820, 1936.

[4] Holt, R. L.: The Pathology of Acute Strangulation of the Intestine. British J. Surg., **21:** 582, 1934.

[5] Hill, F. C., and M. E. Stoner: The Toxicity of Intestinal Content and of the Transudate from an Obstructed Loop. Surgery, **10:** 250, 1941.

[6] von Albeck, V.: Aus gefuhrt am Universitatslaboratorium fur Medicinische Bacteriologie in Kopenhagen. Arch fur Klin. Chir., **65:** 567, 1902.

[7] Wahren, H.: The Intoxication in Intestinal Strangulation: An Experimental Study. Acta chir. Scandinav., **78**: 121, 1936.

[8] Murphy, F. T., and B. Vincent: An Experimental Study of the Cause of Death in Acute Intestinal Obstruction. Boston Med. & Surg. J., **165**: 684, 1911.

[9] McIver, M. A.: Acute Intestinal Obstruction. I. General Considerations. Arch. Surg., **25**: 1098, 1932.

[10] Foster, W. C., and R. W. Hausler: Studies on Acute Intestinal Obstruction; Acute Strangulation. Arch. Int. Med., **34**: 697, 1924.

[11] Scott, H. G.: Intestinal Obstruction; Experimental Evidence on Loss of Blood in Intestinal Strangulation. Arch. Surg., **36**: 816, 1938.

[12] Evans, E. I.: The Mechanism of Shock in Intestinal Strangulation: An Experimental Study. Ann. Surg., **117**: 28, 1943.

[13] Brooks, B., H. W. Schumacher and J. E. Wattenberg: Intestinal Obstruction; An Experimental Study. Ann. Surg., **67**: 210, 1918.

[14] Wilkie, D. P. D.: Experimental Observations on the Cause of Death in Acute Intestinal Obstruction. British Med. J., **2**: 1064, 1913.

FIBROUS DYSPLASIA OF BONE*

JAMES N. PROFFITT, M.D., BARTON MCSWAIN, M.D.,
AND EDMOND H. KALMON, JR., M.D.

NASHVILLE, TENN.

FROM THE DEPARTMENT OF SURGERY OF THE VANDERBILT UNIVERSITY HOSPITAL, NASHVILLE.

OUR INTEREST in fibrous dysplasia of bone was aroused in 1947 by observation of a patient (Case 6) with lesions of the ribs which were thought, on roentgenologic examination, to be cysts. However, exploration of a rib revealed solid tissue, and microscopic examination showed a picture unlike that usually seen in osteitis fibrosa cystica. Comparison of our findings with those described by Albright and his associates[2, 3] and Lichtenstein and Jaffe[32] led us to believe that this patient had the disease which the latter authors called fibrous dysplasia of bone. Subsequently another patient was seen who showed similar roentgenologic, operative and microscopic findings. We reviewed the records, roentgenograms and microscopic sections of all patients seen at the Vanderbilt University Hospital since 1925 who had been diagnosed as having had giant-cell tumor, solitary bone cyst, osteitis fibrosa cystica or Paget's Disease (osteitis deformans). We discovered no cases of fibrous dysplasia previously diagnosed as giant-cell tumor or Paget's Disease but found four instances formerly thought to be osteitis fibrosa cystica and one case originally thought to be a solitary bone cyst. Inasmuch as the status of this syndrome as an entity is still the subject of clinical investigation and few follow-up studies have been recorded, it was thought justifiable to report our observations in seven such patients.

HISTORICAL REVIEW

The first case of what is thought to be the disease under discussion was reported in Europe in 1922 by Wieland.[58] In England, Telford[53] in 1931 reported one "case of osteitis fibrosa with formation of hyaline cartilage" which was probably an example of fibrous dysplasia of bone. Hunter and Turnbull[24] in 1931 reported four cases under the title of focal osteitis fibrosa. In 1932 Braid[6] described such a case and attempted to separate this syndrome from osteitis fibrosa cystica. In this country attention was directed to this syndrome in 1937 when Albright and his associates[2] described five cases of a "syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction with precocious puberty in females." In 1938, Lichtenstein[31] reported similar findings in eight patients and employed the term "fibrous dysplasia of bone."

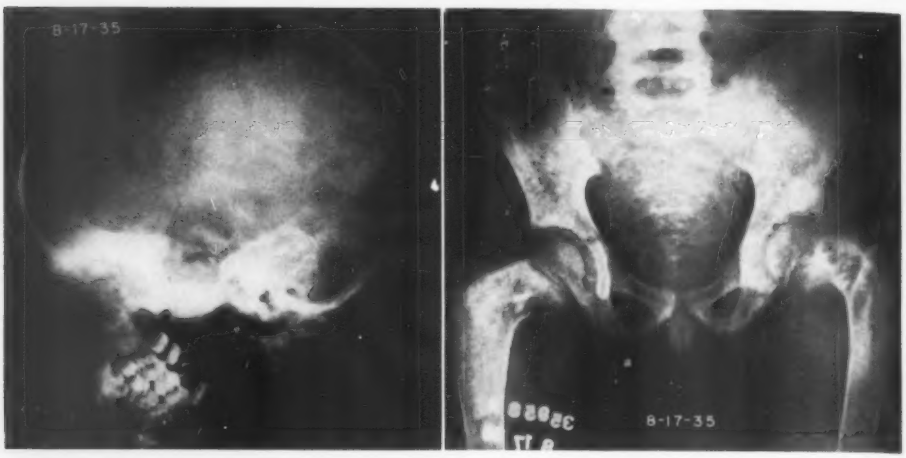
Some of the many terms which have been applied to this disease are Albright's syndrome,[4, 12, 13, 20] polyostotic fibrous dysplasia,[10, 11, 14, 17, 30, 31, 35, 37] osteodystrophia fibrosa,[16, 38, 52] localized von Recklinghausen's disease,[54]

* Submitted for publication April, 1949.

osteitis fibrosa disseminata,[9, 45, 46, 51] regional fibrocystic disease,[1] fibrocystic disease of bone,[22, 42] osteodystrophia disseminata[55] and focal osteitis fibrosa.[24, 53] We have used the term "fibrous dysplasia of bone" because it is the one used by the majority of workers who have recently written about this subject. In view of the many terms applied to this disease it is impossible to discover all such cases which have been reported but the appended bibliography is as nearly complete as possible.

INCIDENCE

Age. The ages of our patients (Table V) on admission ranged from 5 to 61 years. Inasmuch as some observers[15, 17, 25, 26, 28, 30, 32, 34] have stated that



A B

FIG. 1.—Case 1. (A.) There is sclerosis of the bones of the base of the skull, the inferior portion of the frontal bone and the temporal bone. The areas which appear to be rarefied are normal convolutional markings.

(B.) There are areas of rarefaction and spontaneous fracture in each femoral neck with evidence of healing on the right. Other bones involved in this patient are listed in Table I.

this disease usually begins in childhood, it is noteworthy that in one of our patients (Case 2) the age on admission was 61 years and the symptoms were of only two days duration. However, it is obvious that the exact age of onset of his disease could not be determined.

Sex. There were five males and two females.

Race. There were four white and three Negro patients although the ratio of white to Negro patients admitted to the Vanderbilt University Hospital is nine to one. In Schlumberger's[44] report of 67 cases of fibrous dysplasia of bone, only two of the patients were Negroes.

Site. Tables I and II show the sites of involvement of bone.

CLINICAL MANIFESTATIONS

Duration (Table V). The shortest duration of symptoms before admission was two days (Case 2) and the longest was 16 years (Case 6). The other

five patients had had symptoms relating to the disease being reported for one week, three weeks, three and one-half months, seven and eight years.

Symptoms related to bone. There were spontaneous fractures in four patients and the remaining three individuals had pain, although fracture had

TABLE I

Case	Surg. Path. No.	Bones Involved
1	6313	Skull, femora, tibiae, fibulae, radii, humeri, ulnae, 4 metacarpals and 3 phalanges.
2	6601	Upper shaft, left femur.
3	8380	Right 10th rib.
4	10164	Intertrochanteric region, right femur.
5	16285	Left tibia (multiple areas).
6	21577	Left 5th, 6th, 8th and 12th ribs. Right 12th ribs.
7	21914	Right 9th, 10th and 12th ribs.

not occurred. There was disability in all instances, even in the patients with involvement of only the ribs. In the patient with involvement of a bone of the lower extremity in whom there was no fracture, a limp had been present for two days before admission. A tumor had not been noted in any instance.

Age of onset of puberty. Lichtenstein and Jaffe[32] collected 90 cases of fibrous dysplasia, of whom 51 were females, 35 were males, and in four the

TABLE II

	Bones Involved				
	Number of Cases	Number of Bones	Epiphysis	Diaphysis	Metaphyseal Region of Diaphysis
Ribs	3	9	0	..	..
Femur	3	4	0	6	3
Tibia	2	3	0	3	0
Fibula	1	2	0	2	1
Humerus	1	2	0	2	0
Skull	1	1	0	..	..
Ulna	1	2	0	2	0
Radius	1	2	0	3	2
Metacarpals	1	4	0	4	0
Phalanges	1	3	0	3	0
Total	15*	32	0	25	6

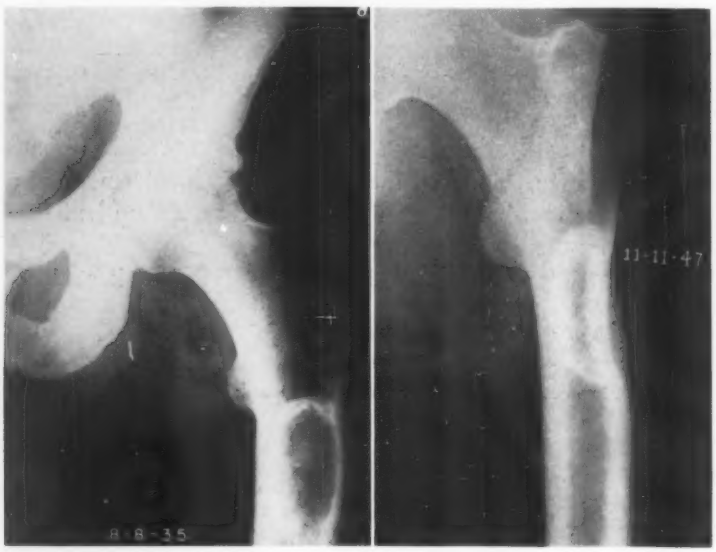
* The apparent discrepancy in the total (15) when there were actually only seven patients, is due to the fact that more than one bone was involved in three patients.

sex was not recorded. Precocious puberty was noted in 20 of the former and in none of the latter. In our two female patients, the menarche occurred at the age of 12 years in Case 5, a Negress, and at 11 years in Case 6, a white woman.

Renal symptoms. None of our patients had symptoms suggestive of renal calculus.

Family history. There was no family history of bone disorder or of neurofibromatosis, but the paternal grandfather of one patient (Case 1) had "brownish splotches" on his back.

Examination of the bones. There was no palpable tumor at the site of involvement of any bone in which there was no fracture. However, tenderness over the diseased areas was present in all seven patients, in four of whom fractures were present. Several authors[2, 3, 12, 15, 17, 18, 25, 37, 43] have observed premature skeletal growth and maturation in girls with the florid form of fibrous dysplasia. Such findings were not present in any of our patients, only two of whom were females and but one of the two (Case 6) having had the disease in the "florid form."



A B

FIG. 2.—Case 2. (A.) There is a lesion of the shaft of the left femur just distal to the lesser trochanter. The cortex is slightly expanded, the margins are quite dense and the lesion is sharply circumscribed. No spiculization is seen. This lesion resembles a latent bone cyst and, although exploration revealed solid tissue, originally the contents may have been cystic.

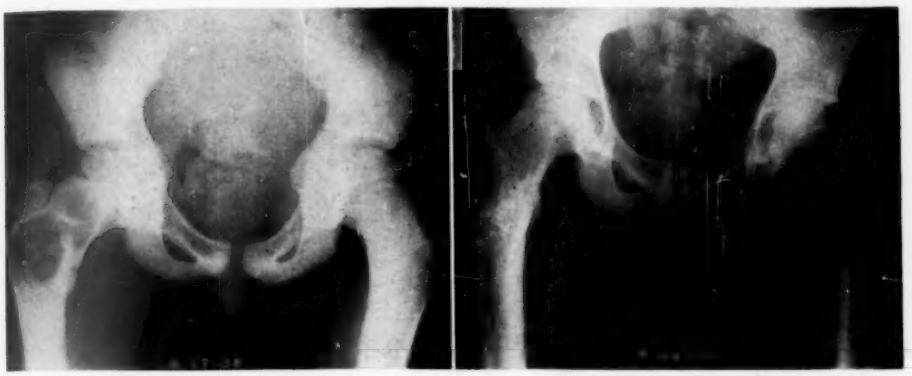
(B.) This film of the left femur made 13 years following curettage and phenol cauterization shows that the area has been almost completely filled in with dense bone.

Skin. Three patients had areas of pigmentation of the skin (Table V). In Case 7, a Negro male, there was an abnormality which we believe has not been described previously in connection with this disease and which may or may not be significant. Just inferior to the left nipple there was markedly decreased pigmentation of the skin (Fig. 6A) over an area 3 by 6 cm. in size. This spot was not elevated and did not differ in texture from the surrounding skin but its appearance was quite striking in contrast to the fairly dark brown skin elsewhere on the body. This patient had fibrous dysplasia of the right ninth, tenth and twelfth ribs.

Thyroid. In 90 cases collected and reported by Lichtenstein and Jaffe[32] hyperthyroidism was present in four patients, one of whom was a male and three of whom were females. Although none of our patients showed evidence of hyperthyroidism, one woman (Case 6) had a basal metabolic rate of minus 23 per cent. She had had six spontaneous abortions with no evident cause other than the hypothyroidism.

ROENTGENOLOGIC FINDINGS

As seen on the roentgenogram, the bone lesions were usually irregular areas of rarefaction which varied greatly in size and shape. In Case 5 (Fig. 4A) there were several small areas measuring only 3 or 4 mm. in diameter,



A B

FIG. 3.—Case 4. (A.) There is a solitary lesion of the neck and upper part of the shaft of the right femur. Spiculization, sharp demarcation and a fracture may be seen. The cortex is expanded.

(B.) This roentgenogram, made more than ten years after the one shown in Fig. 3A shows that most of the area, previously exhibiting decreased density, has been filled in with normal bone. There are four small areas of decreased density.

whereas in Case 3 the pathologic process involved almost the entire length of the tenth rib. The "ground glass" appearance of the rarefied areas usually led the roentgenologists to believe that the lesions were cystic. Bony trabeculae were seen projecting into the areas of increased penetration in all instances except Case 2 (Fig. 2A). In Fig. 6D these trabeculae are clearly shown in the roentgenogram of an excised rib. Except in one instance, there was expansion of the bone with thinning of the cortex in all lesions over 5 mm. in diameter. Case 6 (Fig. 5A) showed disruption of the cortex of a rib. In three patients (Cases 2, 4, and 5) bone of increased density was seen around the margins of the areas of decreased density.

In each of three patients the lesion was single (Figs. 2A and 3A), in one patient there were multiple lesions in a single bone (Fig. 4A) and in three individuals there was involvement of multiple bones (Figs. 1A, 1B, 5A, 5B, 6B and Tables I, II and V).

The portions of the skeleton not involved by fibrous dysplasia showed normal bone structure. In the four patients in whom there were multiple lesions of one or more bones, the bone between the areas of rarefaction appeared normal on the roentgenogram. There was no instance of generalized bone decalcification such as is seen in hyperparathyroidism.

TABLE III

Laboratory Findings

Case No.	Blood Calcium Mgm. %	Blood Phosphorus Mgm. %	Alkaline Phosphatase Bodansky Units	B.M.R. (%)	Calcium Metabolism
1	10.6	2.5	Not done	Not done	Normal
2	11.8	3.12	4.7	4	Not done
3	11.4	3.75	Not done	Not done	Not done
4	11.1	4.6	Not done	Not done	Not done
5	12.7	4.8	5.6	Not done	Not done
6	10.6	3.3	2.7	−21 −23	Normal
7	11.2	3.0	4.4	Not done	Not done

Fractures were seen in four patients, one individual having had fractures of three bones.

In the single patient in whom the skull was involved (Fig. 1A) the bones near its base showed dense sclerosis and thickening. Such findings correspond with those of Furst and Shapiro,[17] Pugh[41] and Windholz.[59, 60]

A tentative diagnosis of fibrous dysplasia of bone should be made if the bone involvement is multiple and predominantly unilateral.

TABLE IV

Operative Findings

Case	Cortex	Color	Consistency	Cysts
1.....	Not recorded	Not recorded	Cartilaginous	None
2.....	Dense	Yellow and grey	Firm, friable	None
3.....	Thin	Whitish	Firm	None
4.....	Not recorded	Reddish	Soft, friable	None
5.....	Thin	Yellow	Friable, gritty	None
6.....	Thin (1 mm.)	Fibrous tissue	Firm, gritty	None
7.....	Thin	Reddish-brown	Firm, rubbery, gritty	One

LABORATORY FINDINGS

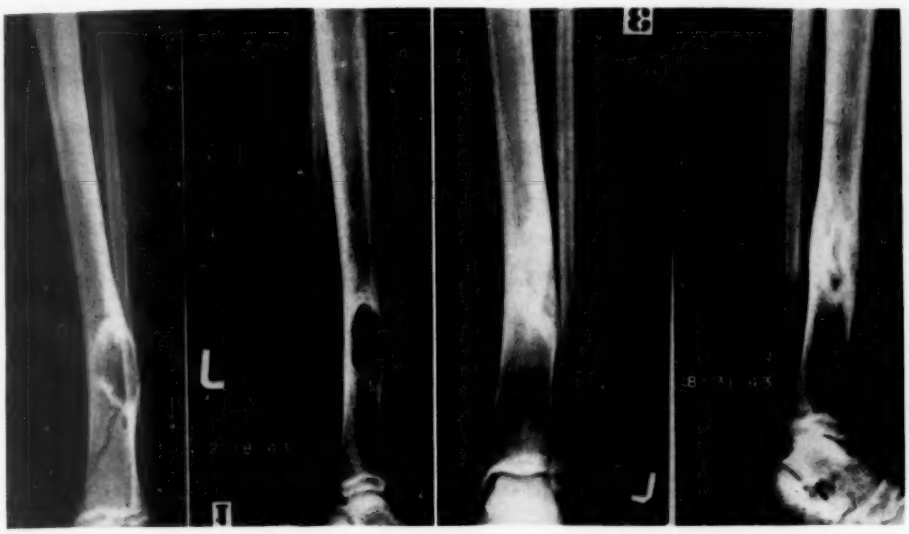
The laboratory studies are shown in Table III. The phosphorus levels were normal and the calcium levels were at the upper limits of normal or slightly elevated.

OPERATIVE FINDINGS AND GROSS PATHOLOGIC CHANGES

After reviewing the clinical manifestations and roentgenograms of his patient, a surgeon who has not previously seen this syndrome usually expects to find at operation a cavity containing fluid. However, in all seven of our patients, exploration of the bone revealed solid tissue and in only one of them

was there any tissue which was not solid. In Case 7, there was a 1.5 by 1 cm. cyst containing yellow fluid but the remainder of the rib showed solid fibrous tissue.

The cortex of the bone was thinned in four of the five instances in which its thickness was described (Table IV). The color of the pathologic tissue varied from white through yellow to reddish-brown, depending upon the amount of hemorrhage which was present. The consistency in one instance was soft and friable but in the others it was firm. The "gritty feeling" due to



A B

FIG. 4.—Case 5. (A.) In the distal portion of the shaft of the tibia there is a large expansile lesion with spiculization and sharply defined, slightly sclerotic margins. In the inferior portion of the rarefied area there is a fracture line which extends distally into the otherwise normal bone. Above the large lesion, several small, round, punched-out areas of decreased density are present.

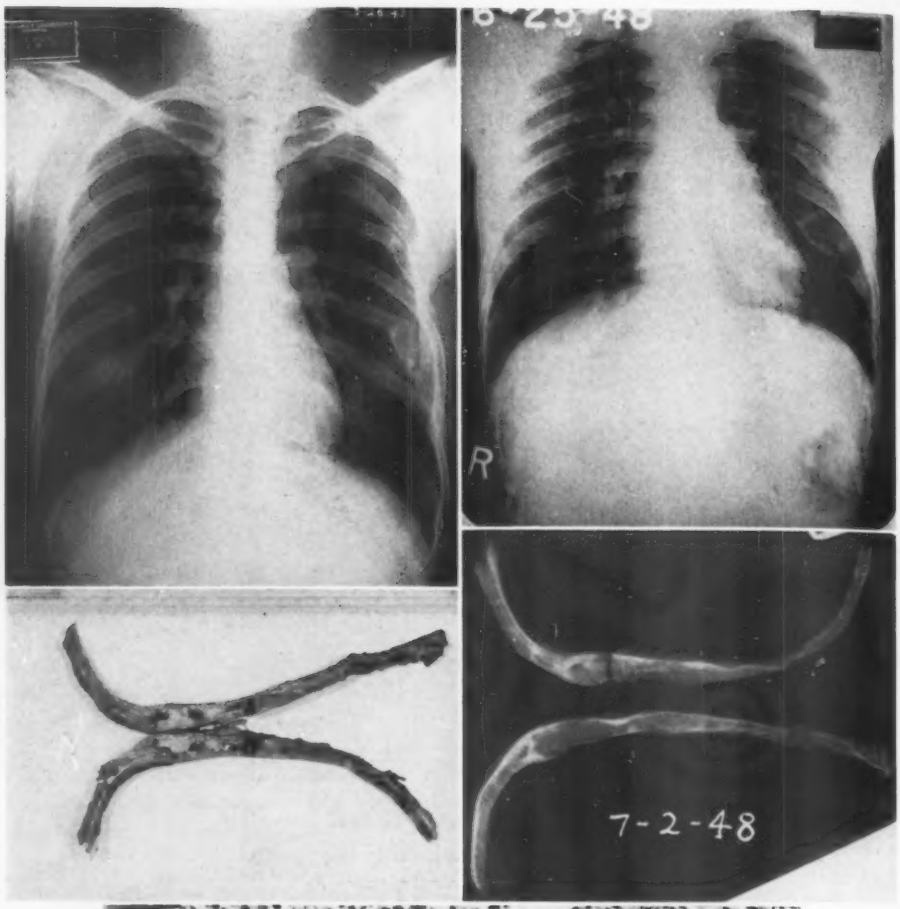
(B.) Six and one-half months after curettage of the large lesion, the roentgenogram shows that the area of rarefaction has become filled in with dense bone and that the fracture has healed.

the presence of spicules of bone was recorded in only three instances but the microscopic sections led us to believe that these spicules must have been present in all of the patients.

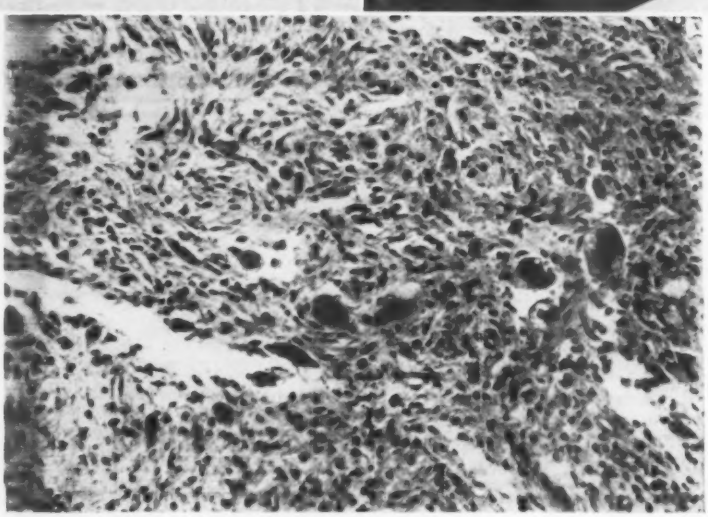
MICROSCOPIC PATHOLOGIC CHANGES

Upon microscopic examination alone, one can positively differentiate fibrous dysplasia from giant-cell tumor, but not from solitary bone cyst or osteitis fibrosa cystica. The two constant findings are connective tissue and osteoid tissue (Fig. 6E). The term "osteoid tissue" is somewhat equivocal; by it we imply that the tissue is young bone which has not been calcified. The areas of new bone formation ranged from acidophilic osteoid tissue to adult calcified bone. In only one instance (Case 6, Fig. 5E) were giant cells seen

A B



C D



E

FIG. 5.—Legends on opposite page

and these cells were readily distinguishable from those seen in giant cell tumor by the fact that their nuclei ranged from two to ten in number instead of from 15 to 200. In the cytoplasm of most of these multi-nucleated cells there were vacuoles varying in number from one to seven. When viewed under polarized light, these vacuoles were seen not to be doubly refractile. In one instance (Case 7, Fig. 6E) the fibrous process was seen extending into the surrounding muscle in the absence of a fracture demonstrable on the roentgenogram. In this patient, the cortex elsewhere was only one millimeter in thickness. Irregular fragments of old bone were seen in several instances. Cartilage other than that which is normally present was not seen.

FOLLOW-UP STUDIES

The follow-up data are presented below and in Table V and Figures 2B, 3B, 4B and 5B.

Case 2. On March 22, 1935, osteotomy of the femur with curettage and cauterization with carbolic acid was done. One month later, the roentgenogram showed some regeneration of bone in the operative area. Three months after operation the roentgenogram showed that there had been some regeneration of bone. Ten months after operation, there was seen on the roentgen ray film almost complete healing of the operative area. On November 11, 1947, more than 12 years after operation, the patient stated that he had had no symptoms referable to the lower extremity or hip. The roentgenogram showed that the previously diseased area had filled in with dense bone (Fig. 2B).

Case 3. On November 18, 1936, the tenth rib was removed. On December 1, 1947, 11 years after operation, the patient stated that he had had no pain in the ribs or any other bones and on that date the roentgenograms of the chest showed no evidence of disease in the remaining ribs.

Case 4. On July 11, 1938, the diseased area in the femur was curetted and bone chips were placed in the cavity. Four months later the roentgenogram showed that the rarefied area, except for about 2 cm., had filled in with normal bone. Nine months after operation, the roentgenogram showed almost complete restoration of normal bony density throughout the femur. On August 28, 1948, (Fig. 3B) more than ten years after operation, there were no symptoms and the roentgenogram showed that most of the formerly diseased area had filled in with normal bone but that there were four small areas of decreased density present.

Case 5. On February 25, 1943, osteotomy with curettage of the tibia was done. Three months later the roentgenogram showed that the fracture had healed. Six months after operation, there was normal function of the extremity and the roentgenogram (Fig. 4B) showed that the large area which previously had shown decreased density was filled in

---

FIG. 5.—Case 6. (A.) This chest film shows lesions of the left fifth, sixth and eighth ribs. Both twelfth ribs were involved also. There has been little change in these lesions since a roentgenogram (not shown) was made elsewhere three years previously.

(B.) The roentgenogram of the chest shows that there has been no change in the lesions of the ribs over a period of fifteen months.

(C.) Photograph of the excised eighth rib which is shown in Fig. 5A.

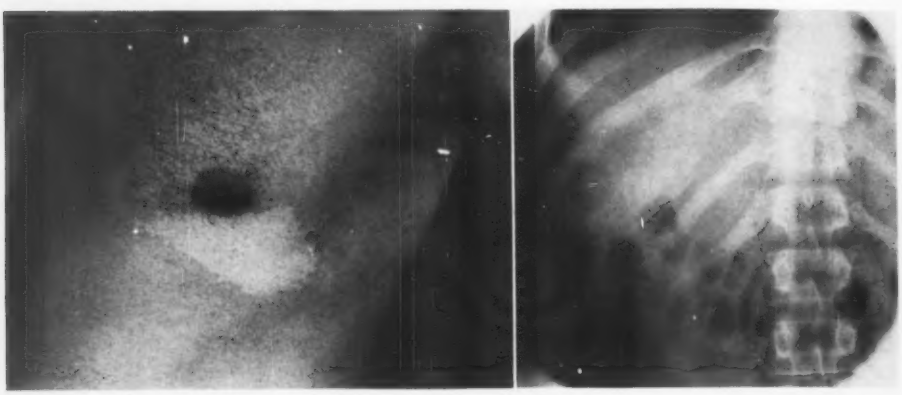
(D.) Roentgenogram of the gross specimen shown in Fig. 5C.

(E.) Multi-nucleated giant cells are shown. There are eight nuclei in the cell just to the left of and below the center of the figure. There are fewer nuclei in the other giant cells.

with dense bone but the small areas of decreased density were still visible. This patient was not seen by us subsequently but in 1947, four years after operation, it was reported by mail that she had had no further symptoms referable to the tibia or any other bone.

Case 6. On March 31, 1947, an osteotomy of the left eighth rib was done and tissue was removed for microscopic study. This patient continued to have pain in the chest, most severe in the region of distribution of the eighth intercostal nerve. On June 25, 1948, the roentgenogram (Fig. 5B) showed that there had been no change since the examination 15 months previously (Fig. 5A). On July 2, 1948, the eighth rib along with the eighth intercostal nerve was excised (Figs. 5C and 5D). The pain decreased immediately after operation and on August 19, 1948, she stated that her pain had been completely relieved.

Case 7. On June 5, 1947, the tenth rib was excised. On June 18, 1948, one year later, the patient stated that he had had no pain. The roentgenogram showed that the



A B

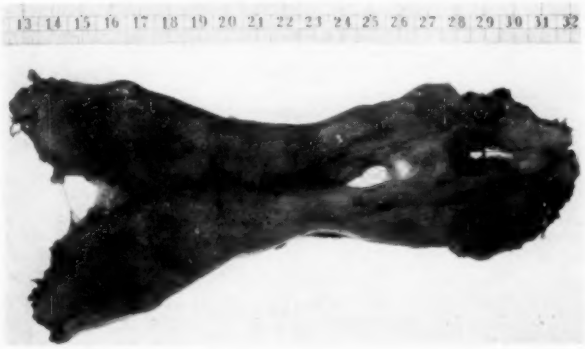
FIG. 6.—Case 7. (A.) Photograph of the area of decreased pigmentation. (B.) There is a large lesion in the right tenth rib which shows expansion of the cortex and extensive spiculization. There is a smaller lesion in the vertebral end of the tenth rib, separated from the more lateral lesion by normal bone. The neck of the ninth and that of the twelfth ribs show rarefaction and trabeculation.

tenth rib had been excised except for the head, in which the diseased area was unchanged, and that there had been no change in the lesions in the ninth and twelfth ribs.

COMMENT

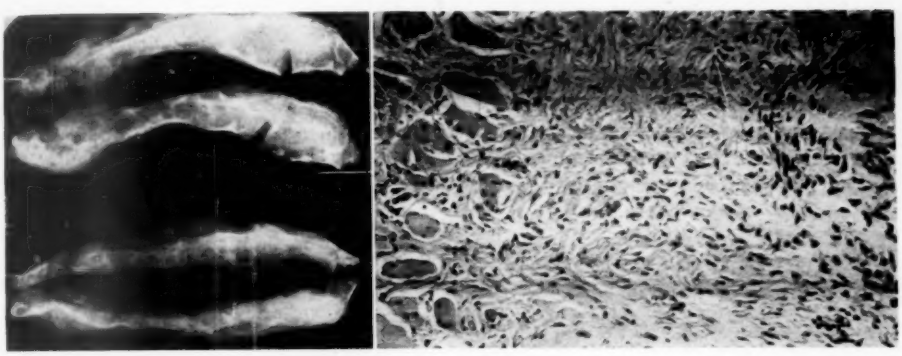
The clinical and roentgenologic manifestations of fibrous dysplasia in a single site and those of solitary bone cyst are almost identical and microscopic examination of the material from lesions of fibrous dysplasia reveals findings quite similar to those seen in the lining of a bone cyst. In both diseases, healing often occurs following spontaneous fracture or curettage. Hence, it is not extremely important to distinguish between these lesions. However, it is necessary to differentiate fibrous dysplasia in its polyostotic form from osteitis fibrosa cystica to prevent the patient's being subjected to a search for a parathyroid adenoma. In three of the seven cases being reported, neck

exploration was done, one of which resulted in death upon the operating table. No parathyroid tumor was found in any of the three patients. The laboratory findings of normal phosphorus levels and calcium levels which are normal or only slightly elevated, plus the operative finding of solid tissue in the bone



C

FIG. 6.—(C.) Photograph of the excised tenth rib.



D E

FIG. 6.—(D.) The roentgenogram of the excised tenth rib shows translucent areas traversed by bony trabeculae. The translucent areas on the roentgenogram, indistinguishable from cysts, were composed of fibrous tissue except for one cyst which was 1.5 by 1 cm. in size.

(E.) On the left there is striated muscle which has been invaded by the fibrous process. The central portion shows connective tissue and the right side shows osteoid tissue.

instead of fluid, are nearly always adequate criteria upon which to make this differentiation. With equivocal findings it may be necessary to demonstrate the absence of negative calcium balance in order positively to rule out the presence of hyperparathyroidism.

Our follow-up studies indicate that the lesions of fibrous dysplasia of bone may remain unchanged for many months or even years and that healing occurs following removal of the fibrous tissue. Recurrence was not noted in

any of our patients nor did sarcoma occur. The question of the frequency with which sarcoma develops in areas of fibrous dysplasia cannot be answered by our studies or by the material thus far reported in the literature. Coley and Stewart[10] reported two cases of sarcoma in patients with fibrous dysplasia. However, microscopic sections from the lesions showed sarcoma from the outset. Jaffe[26] reported a patient in whom "an indubitable osteogenic sarcoma

TABLE V

Summary

Case	Age (yrs.) Onset	Age (yrs.) Admission	Sex	Race	Presenting Symptom	Skin	No. of Bones Involved	Operative Treatment	Result	Length of Time Followed
1	5	5	M	W	Fracture of tibia and both femora	Cafe-au-lait spots on back	20	a) Biopsy of fibula b) Neck exploration	Expired during neck exploration	
2	61	61	M	W	Pain in thigh	Normal	1	a) Biopsy of femur Curettage and phenol cauterization	Lesion filled in with dense bone, symptom-free	13 yrs.
3	25	25	M	C	Pain in chest	Small pigmented area on back	1	Excision of right 10th rib	Symptom-free	11 yrs.
4	8	8	M	W	Fracture of femur	Normal	1	Curettage. Bone chips inserted	Lesion filled in with dense bone, symptom-free	10 yrs.
5	6	13	F	C	Fracture of tibia	Normal	1	a) Curettage. b) Exploration of neck	Lesion filled in with dense bone, symptom-free	5 yrs.
6	12	28	F	W	Pain in chest	Cafe-au-lait spots on back	5	a) Biopsy of rib b) Exploration of neck c) Excision of 8th rib	Improved	16 mos.
7	25	33	M	C	Pain in chest	Depigmented area on back	3	Excision of right 10th rib	Symptom-free	12 mos.

developed in the tibia, which latter still showed evidence of fibrous dysplasia." Up to the time of writing, no report has appeared in which it was stated that exploration revealed fibrous dysplasia and subsequent exploration showed sarcoma.

SUMMARY

The clinical, laboratory, roentgenologic, operative and pathologic manifestations of seven cases and the follow-up studies on six cases of fibrous dysplasia of bone have been presented.

CONCLUSIONS

1. By no one study, that is, clinical, roentgenologic, operative, or pathologic, is it always possible to differentiate fibrous dysplasia from bone cysts and giant-cell tumors.

2. Fibrous dysplasia of bone can be differentiated from other diseases of bone by proper interpretation of the clinical, laboratory, roentgenologic, operative, and pathologic findings.

3. In most instances of multiple bone involvement by fibrous dysplasia, the diagnosis can be made upon the basis of the roentgenologic findings and the calcium and phosphorus levels.

4. Following fracture, healing usually occurs in fibrous dysplasia just as it does in bones in which there are cysts.

5. In long bones, healing with new bone formation occurs following curettage.

6. In a patient with fibrous dysplasia of a rib, if the lesion is accompanied by pain, the rib and intercostal nerve should be excised.

BIBLIOGRAPHY

[1] Adams, C. O., E. L. Compere and J. Jerome: Regional Fibrocystic Disease. Surg., Gynec. & Obst., **71**: 22, 1940.

[2] Albright, F., A. M. Butler, A. O. Hampton and P. Smith: Syndrome Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation and Endocrine Dysfunction, with Precocious Puberty in Females: Report of Five Cases. New England J. Med., **216**: 727, 1937.

[3] Albright, F., W. B. Scoville and H. W. Sulkowitch: Syndrome Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation and Gonadal Dysfunction, Further Observations Including Report of Two More Cases. Endocrinology, **22**: 411, 1938.

[4] Behrend, A.: Albright's Syndrome. Ann. Surg., **121**: 245, 1945.

[5] Bogart, F. B., and A. E. Imler: Fibrous Dysplasia of Bone. Am. J. Roentgenol. and Rad. Therapy, **58**: 478, 1947.

[6] Braid, F.: Osseous Dystrophy Following Icterus Gravis Neonatorum. Arch. Dis. Childhood, **7**: 313, 1932.

[7] Braid, F.: Osseous Dystrophy Following Icterus Gravis Neonatorum. Arch. Dis. Childhood, **14**: 181, 1939.

[8] Bremer, J. L.: Osteitis Fibrosa Localisata: An Experimental Study. Arch. of Path., **32**: 200, 1941.

[9] Coleman, M.: Osteitis Fibrosa Disseminata: Report of a Case. Brit. J. Surg., **26**: 705, 1939.

[10] Coley, B. L., and F. W. Stewart: Bone Sarcoma in Polyostotic Fibrous Dysplasia. Ann. Surg., **121**: 872, 1945.

[11] Denstad, T.: Polyostotic Fibrous Dysplasia. Acta Radiologica, **21**: 143, 1940.

[12] Dockerty, M. B., R. K. Ghormley, R. L. J. Kennedy and D. G. Pugh: Albright's Syndrome. Arch. Int. Med., **75**: 357, 1945.

[13] Dockerty, M. B., H. W. Meyerding and G. T. Wallace: Albright's Syndrome. Proc. Staff Meet., Mayo Clinic, **19**: 81, 1944.

[14] Etter, L. E., and J. W. Hurst: Polyostotic Fibrous Dysplasia. Radiology, **41**: 70, 1943.

[15] Falconer, M. A., and C. L. Cope: Fibrous Dysplasia of Bone with Endocrine Disorders and Cutaneous Pigmentation (Albright's Disease). Quart. J. Med., **11**: 121, 1942.

[16] Freund, E., and C. B. Meffert: On the Different Forms of Non-Generalized Fibrous Osteodystrophy. Surg., Gynec., and Obst., **62**: 541, 1936.

[17] Furst, N. J., and R. Shapiro: Polyostotic Fibrous Dysplasia: Review of the Literature with Two Additional Cases. Radiology, **40**: 501, 1943.

[18] Garlock, J. H.: The Differential Diagnosis of Hyperparathyroidism. Ann. Surg., **108**: 347, 1938.

[19] Ghormley, R. K., and J. J. Hinchey: The Use of Aluminum Acetate in the Treatment of Malacic Diseases of Bone. J. Bone & Joint Surg., **26**: 811, 1944.

[20] Gorham, L. W., E. H. Campbell, W. P. Howard, J. L. Donhauser and N. H. Rust: Albright's Syndrome. Clinics, **1**: 358, 1942.

[21] Hatcher, C. H.: The Pathogenesis of Localized Fibrous Lesions in the Metaphyses of Long Bones. Ann. Surg., **122**: 1016, 1945.

[22] Helfet, A. J.: A New Concept of Parathyroid Function and Its Clinical Application: A Preliminary Report on the Results of Treatment of Generalized Fibrocystic and Allied Bone Diseases and of Rheumatoid Arthritis by Aluminium Acetate. Brit. J. Surg., **27**: 651, 1940.

[23] Hodges, P. C., D. B. Phemister and A. Brunschwig: Diagnostic Roentgenology, Chapt. VI. The Roentgen-Ray Diagnosis of Diseases of Bones. 1936, New York, Thomas Nelson and Sons.

[24] Hunter, D., and H. M. Turnbull: Hyperparathyroidism. Brit. J. Surg., **19**: 203, 1931.

[25] Jaffe, H. L.: Hyperparathyroidism. Bull. of New York Acad. Med., **16**: 291, 1940.

[26] Jaffe, H. L.: Fibrous Dysplasia of Bone. Bull. of New York Acad. Med., **22**: 588, 1946.

[27] Jaffe, H. L.: Fibrous Dysplasia of Bone. J. Mt. Sinai Hosp., **12**: 364, 1945.

[28] Jaffe, H. L., and L. Lichtenstein: Non-osteogenic Fibroma of Bone. Am. Jour. of Path., **18**: 205, 1942.

[29] Jaffe, H. L., L. Lichtenstein and R. B. Portis: Giant Cell Tumor of Bone. Arch. Path., **30**: 993, 1940.

[30] Kornblum, K.: Polyostotic Fibrous Dysplasia. Am. J. Roentgenol., **46**: 145, 1941.

[31] Lichtenstein, L.: Polyostotic Fibrous Dysplasia. Arch. Surg., **36**: 874, 1938.

[32] Lichtenstein, L., and H. L. Jaffe: Fibrous Dysplasia of Bone. Arch. Path., **33**: 777, 1942.

[33] Mallory, T. B.: Medical Progress; Pathology: for, Diseases of Bone. New England J. Med., **227**: 955, 1942.

[34] Mann, A. W., O. Eitzen, and E. P. McNamee: Fibrous Dysplasia of Bone. Am. J. Roentgenol. and Rad. Therapy, **56**: 707, 1946.

[35] Moehlig, B. C., and F. Schreiber: Polyostotic Fibrous Dysplasia: Report of Case with Unilateral Involvement. Am. J. Roentgenol., **44**: 17, 1940.

[36] Murray, R. C., H. J. R. Kirkpatrick and E. Forrai: A Case of Albright's Syndrome. Brit. J. Surg., **34**: 48, 1946.

[37] McCune, D. J.: Osteitis Fibrosa Cystica; The Case of a Nine Year Old Girl Who Also Exhibits Precocious Puberty, Multiple Pigmentation of the Skin and Hyperthyroidism. Am. J. Dis. Childhood, **52**: 743, 1936.

[38] McCune, D. J., and H. Bruch: Osteodystrophia Fibrosa. Am. J. Dis. Childhood, **54**: 806, 1937.

[39] Neller, J. L.: Osteitis Fibrosa Cystica (Albright). Am. J. Dis. Childhood, **61**: 590, 1941.

[40] Osgood, E. C.: Polyostotic Fibrous Dysplasia and Osteopathia Condensans Disseminata. Am. J. Roentgenol. & Rad. Therapy, **56**: 174, 1946.

[41] Pugh, D. G.: Fibrous Dysplasia of the Skull; A Probable Explanation for Leontiasis Ossea. Radiology, **44**: 548, 1945.

[42] Robson, K., and J. W. Todd: Fibrocystic Disease of Bone with Skin Pigmentation and Endocrine Dysfunction. Lancet, **1**: 377, 1939.

[43] Scholder, B. M.: The Syndrome of Precocious Puberty, Fibrocystic Bone Disease, and Pigmentation of the Skin. Ann. Int. Med., **22**: 105, 1945.

[44] Schlumberger, H. G.: Fibrous Dysplasia of Single Bones. Mil. Surgeon, **99**: 504, 1946.

[45] Shallard, B. T.: Osteitis Fibrosa Disseminata. M. J. Australia, **1**: 558, 1940.

[46] Snapper, I.: Lipoid Granulomatosis of the Bones. Xanthomatosis of the Bones. Chap. V., Medical Clinics on Bone Diseases. New York, Interscience Publishers, 1943.

[47] Snapper, I., and C. H. Parisel: Xanthomatosis Generalisata Ossium. Quart. J. Med., **2**: 407, 1933.

[48] Sosman, M. C.: In Discussion of Pugh.[41]

[49] Stauffer, H. M., R. K. Arbuckle and E. E. Aegerter: Polyostotic Fibrous Dysplasia with Cutaneous Pigmentation and Congenital Arteriovenous Aneurysms: Case. J. Bone & Joint Surg., **23**: 323, 1941.

[50] Stauffer, H. M., and P. J. Fitzgerald: Fibrous Dysplasia—A "Cystic" Lesion of Bone. U. S. Naval Med. Bull., **45**: 653, 1945.

[51] Sternberg, W. H., and V. Joseph: Osteodystrophia Fibrosa Combined with Precocious Puberty and Exophthalmic Goiter. Am. J. Dis. Childhood, **63**: 748, 1942.

[52] Summerfeldt, P., and A. Brown: Osteodystrophia Fibrosa. Am. J. Dis. Childhood, **57**, 90, 1939.

[53] Telford, E. D.: Case of Osteitis Fibrosa with Formation of Hyaline Cartilage. Brit. J. Surg., **18**: 409, 1931.

[54] Thannhauser, S. J.: Neurofibromatosis (Von Recklinghausen) and Osteitis Fibrosa Cystica Localisata et Disseminata (Von Recklinghausen). Medicine, **23**: 105, 1944.

[55] Thomas, H. W., T. N. Meredith and H. L. Wunderly: Osteodystrophia Disseminata: Case. J. Pediat., **18**: 638, 1941.

[56] Ulland, G.: Polyostotic Fibrous Dysplasia—Albright's Syndrome. Acta Chir. Scandinav., **89**: 113, 1943.

[57] White, E. H.: Polyostotic Fibrous Dysplasia. Surgery, **11**: 607, 1942.

[58] Wieland, E.: Osteitis Fibrosa Cystica Congenita. Arch. f. Kinderheilkunde, **71**: 241, 1922.

[59] Windholz, F.: Cranial Manifestations of Fibrous Dysplasia of Bone. Am. J. Roentgenol. & Rad. Therapy, **58**: 51, 1947.

[60] Windholz, F.: Osteoporosis Circumscripta Cranii, Its Pathogenesis and Occurrence in Leontiasis Ossea and in Hyperparathyroidism. Radiology, **44**: 14, 1945.

CARCINOMA OF THE LOWER LIP*

A TEN YEAR SURVEY

SAM Z. MAROON, M.D. AND ROBERT H. KENNEDY, M.D.

NEW YORK, N. Y.

FROM THE TUMOR DIVISION, SKIN AND CANCER UNIT, NEW YORK POST-GRADUATE MEDICAL SCHOOL AND HOSPITAL

DIVERSITY OF OPINION EXISTS in the literature as to the manner of treatment of carcinoma of the lip. The pros and cons of prophylactic neck dissection have been reported by Kennedy[1] and McClure.[2] We shall not add to the arguments in this presentation but simply review the cases of epitheliomata of the lower lip which have come to operation, and the follow-up results obtained on the Tumor Division of the New York Post-Graduate Hospital.

The difficulty in evaluating the various forms of treatment of this condition is due in part to the inadequate and incomplete follow-up in this type of patient. In addition, the life expectancy of patients in this age group is lessened by the high incidence of intercurrent diseases.

Kennedy[3] has described the routine followed at this clinic for management of carcinoma of the lip. In general, in patients treated since 1938, this pattern has been followed. A review of these cases, numbering 119, which were operated upon follows.

Of these 119 cases of carcinoma of the lower lip, four were found in women. The age distribution is shown in Figure 1. There was one case in a man 23 years old. Sixty-one per cent occurred in the sixth and seventh decade of life.

The duration of the lesion as stated in 114 cases is as follows:

1 mo..... 6	4 mos..... 10	7 mos..... 6	10 mo.–1 yr..... 8
2 mos..... 11	5 mos..... 4	8 mos..... 4	1 yr. –2 yrs..... 17
3 mos..... 17	6 mos..... 13	9 mos..... 4	Over 2 yrs..... 14

One half of the cases presented themselves before six months, and fully one third of the lesions were at least ten months in duration.

The pathologic diagnosis in all 119 cases was squamous cell carcinoma: 79 were of grade I, 14 of grade II, and five of grade III. Twenty-one were not graded. In only nine cases was the lesion larger than 3 cm. There was no correlation between length of history and size of the lesion, and the duration of these nine cases was well under nine months. There was no relationship between size and grade, and four of the five grade III lesions had lymph node metastases.

Cervical node specimens were obtained in 95 of the cases. Of 58 patients in whom nodes were palpable, involvement was found by microscopic section in 14 cases. In the remainder of the nodes a diagnosis of chronic lymphadenitis was made. Complete regression of epidermoid carcinoma metastases

* Submitted for publication January, 1949.

in cervical nodes from external radiation alone has been reported by some authors. In light of the above findings and similar findings in other series, and since it is impossible clinically to differentiate for certain a metastatic node from an inflammatory one, *the results of radiation must remain inconclusive unless nodes are removed.*

Four cases of positive node involvement were found in which nodes were not palpable preoperatively. Thus, absence of palpable nodes does not mean

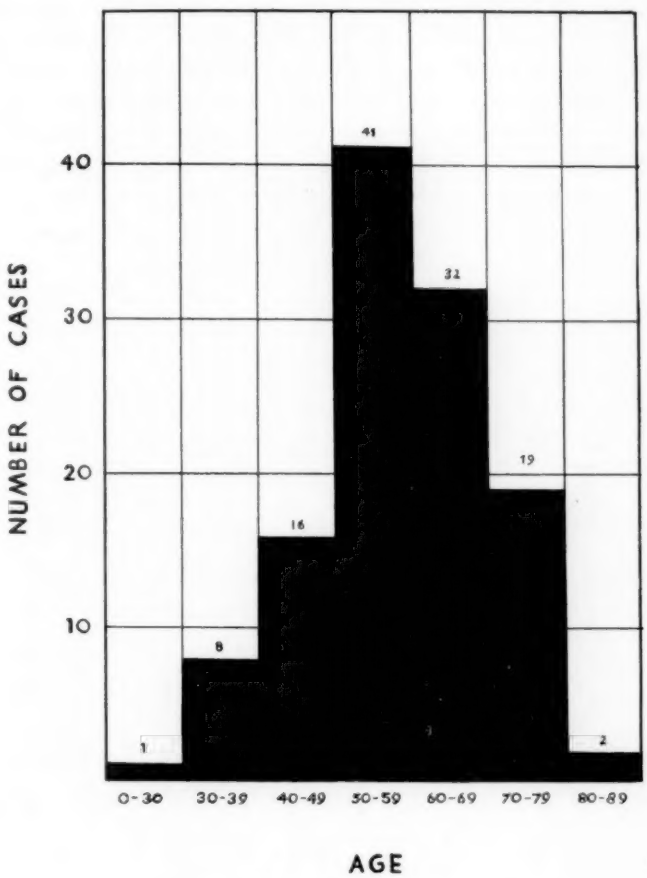


FIG. 1.—Age distribution.

absence of metastases. Kennedy[3] has pointed out previously that the absence of pathologic evidence of metastases does not necessarily mean absence of metastases. In general we agree that it is impossible to decide whether an enlarged node is involved or not, and certainly involvement may occur without palpable enlargement. In light of this, it is debatable whether frequent follow-up examinations offer assurance to the patient as to the time operative incision of the drainage area is indicated.

The surgical procedures used in these patients are as follows:

Local excision alone	24
Local excision plus suprahyoid neck dissection (5 of these had further neck dissections)	79
Local excision plus omohyoid neck dissection (1 of these had further neck dissection)	14
Local excision plus complete neck dissection, unilateral	1
"Commando" type operation with partial resection of lower jaw	1

LOCAL EXCISION

Local excision alone was performed on 24 patients. The operation was usually a "V" excision (19 cases) but, when the growth was large, adequate excision plus plastic repair was performed (five cases).

In one instance a local excision alone was performed for palliation in a far advanced case with metastases to the lung. This patient expired one month later. It was planned to do a prophylactic neck dissection in the remaining 23 cases, as is the policy at this clinic, but these patients either refused further operation or failed to return for additional operative procedure.

The follow-up results in these 23 cases is as follows:

(a) Alive and well	16
(b) Alive with possible metastases present, lost to follow-up	2
(c) Dead of undetermined cause	3
(d) No follow-up	2

(a) Fifteen of the 16 patients who were alive and well at the last follow-up visit had no evidence of recurrence for the following length of time:

9 yrs.	1 case
6 yrs.	1 case
4 yrs.	1 case
3 yrs.	4 cases
2 yrs.	3 cases
½ yr.	5 cases

The other patient developed local recurrence two years later. The lesion was re-excised two years after that and the patient was followed for an additional year without evidence of recurrence, local or otherwise. It is noteworthy that in all but two of these 16 patients who were alive and well at the last follow-up, there were no palpable nodes preoperatively. The two patients with palpable nodes in the submaxillary region were among those who were followed for the one-half year period only.

(b) Two patients developed large palpable masses in the neck six months following excision but failed to return for further treatment. These two patients had palpable nodes preoperatively.

(c) Three patients died two years, six months, and three months respectively postoperatively from undetermined causes. There was no evidence of recurrence of carcinoma in that time.

(d) In two cases there was no follow-up. These had palpable nodes.

In this group of 23 cases in which local excision was done preliminary to intended prophylactic neck dissection, it is interesting to note the follow-up in the seven cases of the group who had palpable nodes. Of the five who were followed, one died three months later from undetermined cause, two were those who developed cervical masses six months later, and two had no evidence of enlargement six months following excision.

No definite conclusions can be drawn from the material available in this group. Certainly patients with enlarged nodes should have definitive treatment instituted to eradicate possible cervical node involvement.

LOCAL EXCISION PLUS SUPRAHYOID NECK DISSECTION

Seventy-nine cases had local excision plus suprahyoid neck dissection, 66 of these at one operation. In the majority of instances the neck dissections were performed bilaterally. Aside from the fact that many of the lesions occur in the middle one-third, in which cases a bilateral dissection is indicated, we feel that a better cosmetic result can be obtained if the dissection is carried out on both sides. In 12 cases positive evidence of metastases in the nodes was found, and in five of these additional cervical node dissection was done. There were no operative deaths.

In the 67 cases with negative nodes, follow-up was available in 64 cases. 59 had no recurrence in the time followed as indicated below:

9 yr.	2	4 yr.	5
8 yr.	4	3 yr.	11
7 yr.	2	2 yr.	10
6 yr.	6	1 yr.	8
5 yr.	6	½ yr.	5

One patient died one year later, presumably from carcinoma. Four patients died from causes other than carcinoma. Two of the latter lived six years and five years respectively postoperatively, and had no evidence of recurrence.

In the 12 cases with positive nodes, five underwent further surgical procedures:

Further Procedure	Nodes	Follow-Up
Right omohyoid	Negative	5 years. . . . . no recurrence
Bilateral omohyoid	Negative	Died 2 yr. . . . . cause undetermined
Left omohyoid	Positive	Died 6 yr. . . . . carcinoma
Left complete	All nodes positive	Died 1½ yr. . . . . cause undetermined
Bilateral complete	All nodes positive	Died ½ yr. . . . . cause undetermined

Seven cases had no further surgery. Of five cases followed, four lived three years without recurrence, and one died one and one-half years later after receiving roentgen ray treatment as a palliative measure.

Of five patients with positive nodes removed in suprahyoid dissection in whom further surgery was done, three were found to have positive nodes below the suprahyoid region. The prognosis in all cases where suprahyoid nodes are found involved is poor. In ten cases followed, only six patients were alive after three years. One of these died at six years. It would seem that the time margin of safety is small once nodes are involved. In 64 cases followed for varying periods after suprahyoid neck dissection and in whom nodes were negative, there was only one known death from carcinoma, occurring one year postoperatively.

LOCAL EXCISION PLUS OMOHYOID NECK DISSECTION

Local excision plus resection of nodes above the omohyoid crossing was performed in 14 patients. One required additional cervical node dissection. There were no operative deaths.

In ten of these cases, the excised nodes were negative for metastases. Six of these patients had palpable nodes on physical examination. In the follow-up of these patients there was no known recurrence of the carcinoma. Nine were followed for variable times as shown:

9 yr.	3	2 yr.	2
4 yr.	1	1 yr.	2
3 yr.	1		

Four of the 14 cases had positive nodes. Three were limited to nodes in the suprahyoid region of the neck. One of these was followed ten years and one was followed four years without evidence of recurrence. The third case, a lesion of grade II, developed a recurrence in the neck one year postoperatively, had further neck dissection to the clavicle, and died one year later.

In one case of initial omohyoid dissection all the nodes removed above and below the level of the hyoid bone were found to be involved. This patient developed a large cauliflower mass in the neck six months later and no further follow-up was obtained. This lesion was of grade III.

There is no evidence of recurrence of carcinoma in those cases in which prophylactic omohyoid neck dissection was done and negative nodes were found. Two of the four cases with positive nodes undoubtedly died of the carcinoma. These lesions were of a more malignant variety as indicated by the grade.

One patient, age 75, had a local excision plus unilateral complete neck dissection. The tumor was found to involve all the nodes of the neck that were removed and extended to the adventitia of the internal jugular vein. This patient died on the first postoperative day from pulmonary edema. This was the only operative death in the entire series.

Another extensive case required a partial resection of the right mandible, together with a complete neck dissection. This patient lived only six months following the operation.

SUMMARY

1. A review of 119 cases of carcinoma of the lower lip treated surgically at this clinic since 1938 is presented.

2. Neck dissections of various magnitudes were done in 95 of these cases in conformity to the routine here. There was one operative death in a man 75 years of age who had extensive involvement and in whom a complete unilateral neck dissection was done.

3. Nodes were found positive for malignancy in 18 of the 95 cases in whom cervical node dissections were done. In 77 cases, the nodes were found free of malignancy on microscopic examination. The follow-up results in these 2 groups of patients is as follows:

	Negative Nodes (77)	Positive Nodes (18)
Well for 5 years	25	2
Follow-up for less than 5 years and well	47	5
Died of carcinoma	1	5
Dead from cause undetermined	0	4
Lost to follow-up	4	2

There was one known death from carcinoma among those cases in whom nodes were removed and found histologically negative for metastases. The prognosis in these cases is good. Once the regional nodes are involved, the prognosis as judged from available follow-up becomes much worse in spite of radical neck dissections. When nodes become initially involved, the time factor of safety seems to be small, since further node group involvement is the rule.

4. In light of the extremely low mortality of neck dissections, the uniformly good results obtained in available follow-up when nodes removed were found to be negative, and the relatively poor results obtained once nodes are involved, it would seem that prophylactic neck dissection in cases of carcinoma of the lip is strongly indicated.

BIBLIOGRAPHY

[1] Kennedy, Robert H.: Ann. Surg., **114**: 813, 1941.
[2] McClure, Roy D., and Conrad R. Lam: Ann. Surg., **125**: 658, 1948.
[3] Kennedy, Robert H.: Ann. Surg., **106**: 577, 1937.

PRIMARY CARCINOMA OF THE URETER*

FRANCIS G. HARRISON, M.D., HERBERT L. WARRES, M.D.
AND JOHN A. FUST, M.D.

PHILADELPHIA, PA.

FROM THE DEPARTMENT OF UROLOGY AND THE LABORATORIES, PRESBYTERIAN HOSPITAL: AND THE GRADUATE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA

WHILE PRIMARY CARCINOMA OF THE URETER is not a common tumor, it no longer can be regarded as rare. In 1934, Lazarus[12] was able to collect only 68 cases from the literature of the preceding 90 years. Nine years later, however, Scott[19] found 182 and Sauer[18] 189. In 1948, Gulatieri, Hayes and Segal[9] collected 196 cases and added two of their own. We wish to report seven additional cases.

CASE REPORTS

Case 1.—C. H., Record No. 24259, a 59-year-old white male, was admitted on September 9, 1936, because of hematuria. The patient had his first attack of gross hematuria in 1934. This stopped in one day under bromide and citrate therapy. No further bleeding occurred until two months prior to admission, when it again responded within a day to the same therapy. Cystoscopy done at that time revealed inflammation of the right ureteral orifice, obstruction of the ureter 4 cm. above the orifice, and a non-functioning kidney. On both occasions there was gross bleeding accompanied by clots but no pain. For the past 25 years the patient had occasional attacks of gnawing pain in the right lower quadrant which had been diagnosed as chronic appendicitis.

Physical examination was entirely normal. B.P. 140/80. Urinalysis was negative except for a trace of albumin. Hb. 85 per cent; rbc 4.5 million. Wbc 7,200. BUN 15. A chest roentgenogram was not remarkable.

A diagnosis was made of neoplasm of the right kidney. On September 10, a transperitoneal right nephrectomy and appendectomy were done. The right kidney contained 500 to 600 cc. of clear urine. The ureter passed through a rough, hard, egg-sized mass which involved the appendix. The mass, appendix, and kidney were removed.

Pathology report. "Gross: The kidney is hydronephrotic. The ureter is surrounded by a 6 by 6 by 3 cm. firm, fairly well encapsulated mass involving the tip of the appendix. Microscopic: The bulk of the tumor consists of fibrous stroma which surrounds sheets and strands of epithelial cells, most of which are polyhedral and tightly packed. Scattered cells are large and round, sometimes bizarre, and frequently show kerato-hyaline granules and abortive pearl formation. The appendiceal wall has been infiltrated by tumor cells but the lumen is obliterated by fibro-adipose tissue. The ureter is recognized by the remnants of the smooth muscle of its wall. Lymphatic permeation is noted. Diagnosis: Moderately undifferentiated squamous cell carcinoma of the ureter (Carcinoma, grade III); hydronephrosis."

The postoperative course was complicated by right thrombophlebitis. The patient was given a course of deep roentgen ray therapy and discharged October 2, 1936.

C. H. was re-admitted on January 10, 1937, complaining of weakness (three months duration), anorexia (two months), constipation (two months), and fecal vomiting (12 to 14 hours).

* Submitted for publication April, 1949.

Positive findings on physical examination were as follows: T. 99°F. B.P. 150/90. The abdomen was distended and tympanitic. There was a hard, fixed, plum-sized mass on the right, midway between the umbilicus and anterior superior iliac spine. Another hard mass, slightly larger, was present just below and slightly to the right of the navel. The right leg was swollen and slightly tender.

Urinalysis was negative. Hb. 80 per cent; rbc 3.8 million. BUN 37.

On January 11 a laparotomy was done. Hard masses were present in the abdominal wall, the veins of which were engorged. A hard fibrous mass was adherent to the spine and lower ileum. The liver was studded with nodules. The ileum was anastomosed to the colon near the hepatic flexure and an ileostomy done. The patient was given additional deep roentgen ray therapy and discharged February 1. The patient died at home on March 4, 1937, of generalized carcinomatosis. An autopsy was not performed.

Comment. This case illustrates the fact that the hematuria associated with these cases may stop for weeks or months under non-specific treatment. Frequently this results in delaying adequate study of the patient. This case was unusual in that the carcinoma of the ureter involved the appendix and later caused intestinal obstruction.

Case 2.—N. B. M., Record No. 30744, a 58-year-old white female, was admitted on June 29, 1937, because of hematuria. The patient had first noticed hematuria associated with frequency and nocturia in 1935. She was admitted to Temple University Hospital. A letter from Dr. W. Wayne Babcock stated that on October 22, 1935, the right ureter just below the renal pelvis had been resected because of a papillary tumor 1 cm. in diameter. The ureter was re-anastomosed to the pelvis with wire sutures.

Review of a slide kindly sent to us by Dr. Ernest E. Aegerter showed a papillary transitional cell carcinoma showing occasional mitotic figures and little tendency to invasion, which we interpreted as papillary carcinoma, grade I.

In the early part of 1937 the patient again noticed hematuria. She entered this hospital for a nephrectomy. Past history revealed that a vaginal hysterectomy had been done in 1929, because of a suppurating cystadenocarcinoma of the right ovary. At that time the specimen showed no microscopic evidence of the ovarian tumor penetrating the peritoneum.

Except for old rheumatic heart disease, physical examination was negative. B.P. 110/80. Urinalysis disclosed marked albuminuria, many pus cells, and occasional red cells. A diagnosis of pyelonephritis secondary to postoperative uretero-pelvic stricture was made.

On June 30, 1937, a right nephrectomy was done, and the patient was discharged on July 21, 1937.

Pathology report. "Gross: The kidney weighs 85 Gm. and displays a narrow cortex. The region from which the tumor is said to have been removed at a previous operation shows nothing unusual. Microscopic: Section through the region from which a tumor had previously been removed does not show any malignant change. The medulla and cortex show areas of polymorphonuclear infiltration and in one area there is a small abscess. Diagnosis: Acute suppurative nephritis."

The patient was re-admitted on January 12, 1943. Six months after her nephrectomy in 1937, she began to have hematuria. Cystoscopy revealed papillomata of the bladder which were fulgurated. Thereafter the patient had recurrences of hematuria and papillomata requiring fulguration every 3 to 4 months.

In November, 1942, she began having attacks of weakness. The hematuria had become almost constant but did not consist of bright red blood or clots. She complained of generalized aching, upper abdominal pain, dyspnea, and palpitation. There had been a weight loss of 15 to 25 lbs. in the past 6 months.

Physical examination differed from the previous one as follows: B.P. 172/112. The liver was 3 finger-breadths below the costal margin and was hard, nodular and nontender. There were no other palpable masses.

Urinalysis was negative. Hb. 13 Gm.; rbc 4.4 million. Wbc 13,600; N 76 per cent, E 8 per cent, L 16 per cent. Sedimentation rate 94. BUN 16. Liver function tests were within normal limits.

Roentgenograms of the chest and abdomen revealed no metastasis to the spine. Barium enema revealed displacement of the colon by the large liver.

On February 3 an exploratory laparotomy was done. Nodules were present in the liver and retro-peritoneal lymph nodes. On the right side, occupying the region of the ureter, there was a sausagelike, hard, nodular mass extending from the level of the umbilicus down into the pelvis. Cystoscopy showed multiple papillomata of the bladder.

The patient gradually went downhill. On February 27 she had marked oliguria due either to obstruction or a hepato-renal syndrome. She died March 1, 1943. Autopsy diagnosis was as follows: Transitional cell carcinoma, moderately undifferentiated of ureter, metastatic in retroperitoneal lymph nodes, liver, mesentery, and lungs.

Comment. Although all of the involved ureter was supposedly excised in 1935, the patient developed papillomata of the bladder and stump of ureter. This points towards a multi-centric origin of these tumors.

Case 3.—W. E., a 63-year-old white male was first seen at the Urologic Clinic on November 10, 1938, with a chief complaint of hematuria. Painless intermittent hematuria had started two months prior to admission. Physical examination was essentially negative.

Cystoscopy on November 10 revealed a pedunculated 3 cm. growth in the vicinity of the left ureteral orifice. The tumor was electro-coagulated. The base was again fulgurated on November 17.

Cystoscopy on January 27, 1939, revealed a small papillary growth around the left ureteral orifice and two small papillomata above and to the left of this orifice. These were fulgurated. Numbers 5 and 6F catheters met an obstruction at 9 cm. up the left ureter. An attempt was made to do a retrograde pyelogram but no radio-opaque medium could be visualized on the left side. An excretory urogram disclosed a non-functioning left kidney. Another retrograde pyelogram was attempted on January 28 without success.

Cystoscopy on May 9, 1939, demonstrated 12 ounces of residual urine. There were two papillomata, each about 1 cm. in diameter, around the left ureteral orifice. The entire vesical neck was the site of papillary growths. These had extended into the prostatic urethra.

On June 9 a suprapubic cystotomy was done. Multiple growths covered the vesical neck, trigone and prostatic urethra. The right ureteral orifice was not involved and spurted clear urine. The left ureter was split upward and the lower portion found filled with papillomata. All the growths were fulgurated.

Pathology report. "Gross: Specimen consists of three small masses of soft, lobulated brown tissue. Microscopic: Protruding from the bladder mucosa are papillary stalks of various diameters which bear masses of moderately undifferentiated transitional type epithelium. The latter shows moderate mitotic activity, with occasional atypical figures, and a distinct tendency to infiltrate underlying structures. Diagnosis: Moderately undifferentiated transitional cell carcinoma of bladder (Papillary carcinoma, grade III).

On June 26 a left nephrectomy was done. The kidney was markedly adherent. The ureter, four times normal in size, was severed below the pelvic brim.

Pathology report. "Gross: The 8 by 5 by 3 cm. kidney has a mottled surface and is hydronephrotic. Two pyramids are thickened by firm, white, partially encapsulated

tissue. In four-fifths of its length, the ureteral mucosa and muscularis are both apparently involved by soft, granular, white tissue. Microscopic: Sections of the kidney show nodules of rather undifferentiated transitional cell epithelium. Small fragments of the latter are seen in lymphatic channels. Other areas of the kidney show marked infiltration by lymphocytes, plasma cells, and eosinophiles. The ureter is lined by neoplastic epithelium similar to that of the bladder although the invasiveness of this tumor is less marked. Diagnosis: Moderately differentiated transitional cell carcinoma of ureter (Papillary carcinoma, grade III). Transitional cell carcinoma, metastatic, of kidney. Hydronephrosis and pyelonephritis.

A chest film on October 4 revealed bilateral pulmonary metastases. The patient died on November 2, 1939.

Comment. In all cases of bladder papillomata, the upper urinary tract should be studied. This is especially true if a ureteral orifice is involved. Obstruction to the passage of a catheter is one diagnostic sign indicating involvement of the ureter.

Case 4.—Z. G., Record No. 63606, a 60-year-old white male, was admitted on December 29, 1941, with a chief complaint of low back pain of five months duration. The pain was most prominent over the coccyx and worse upon walking.

Physical examination revealed the following: B.P. 190/110. The liver edge was just palpable. The prostate was moderately enlarged and non-nodular. Reflexes were sluggish in the lower extremities but no pathological reflexes were present.

Urinalysis was negative except for 2 plus albuminuria. Hb. 14.1 Gm.; rbc 4.1 million. Wbc 7,400; N 75 per cent, E 1 per cent, L 23 per cent, M 1 per cent. Sedimentation rate 44 mm/hr. BUN 14. Acid phosphatase 1.73 Gutman units. Serology negative. Lumbar puncture revealed both pressure and spinal fluid to be normal.

A urological consultation disclosed the following: Frequency, burning, dribbling, difficulty in starting the stream, and nocturia 2X of five months duration. During this same period, the patient suffered severe sharp, constant low back pain. A transurethral resection had been done on November 24, 1941, with some relief of symptoms. Prostate, grade I, enlarged, firm and smooth. There was no tenderness on manipulating the prostate or coccyx. Prostatic secretions were loaded with pus cells. A stricture was present just inside the meatus. This was dilated from 12 to 20F and cystoscopy done. Two ounces of residual urine were present. There was some enlargement of both lateral lobes with anterior notching and a slight median bar. Indigocarmine appeared in 5 minutes from the right ureteral orifice but none from the left. A 6F catheter was passed 27 cm. on the right. No catheter could be passed beyond 3 cm. on the left.

Roentgenograms of the chest and abdomen revealed no evidence of metastasis. Osteoarthritic changes were present at the apophyseal joints between L3 and 4. Retrograde pyelogram showed a somewhat irritable right kidney consistent with chronic pyelonephritis. No radio-opaque medium was present on the left side. An excretory urogram demonstrated less irritability than previously on the right and no function on the left. Diagnosis: Tumor of left ureter with secondary hydronephrosis.

Sigmoidoscopy and barium enema were negative. The orthopedic consultant believed the pain was of neurological origin. On February 11, 1942, a left nephro-ureterectomy was done.

Pathology report. "Gross: The kidney is hydronephrotic. The ureter is dilated as far as a mass palpable in its lower end. After opening the ureter, a firm, irregular, grayish-white tumor mass 4 by 1.5 cm. is seen to arise from the mucosa. Microscopic: The ureter, apart from the tumor proper, is lined by transitional epithelium showing neoplastic

change, the cells being hyperchromatic and forming a pseudostratified structure. The tumor above this grows into the lumen and completely obliterates it. There is rich invasion of lymphatic and venous channels. Diagnosis: Moderately undifferentiated transitional cell carcinoma of ureter (Papillary carcinoma, grade III)."

Postoperatively the patient continued to have coccygeal pain. Roentgen ray of the chest, pelvis and upper femora revealed no metastasis. Injection of the 3 left sacral foramina with procaine relieved the pain temporarily. Injections of ammonium sulfate were given with relief of pain. He was also given a full course of deep roentgen ray therapy. The patient was discharged March 30, 1942.

He was re-admitted on May 10, 1942, because of continued back pain which radiated down the left leg. Otherwise his general condition seemed good. Physical examination was the same as previously with the following exceptions: B.P. 200/110. Pain was present over L3, 4, S1, 2, 3, and C1. There were no changes in heat, cold or position sensation. No pathological reflexes were present. Urinalysis was negative. Hb. 7.8 Gm.; rbc 2.6 million. Wbc 9,900; N 66 per cent, L 34 per cent. BUN 9.

Following a bilateral chordotomy on May 11, the patient developed paralysis of the lower extremities and loss of sphincter control. He was discharged on October 31, 1942, and died four months later.

Comment. This case indicates that pain from tumor metastases may be one of the first symptoms. Though the tumor may grow slowly locally, it frequently penetrates the thin ureteral wall early. Probably the urinary symptoms were partially due to a secondary chronic pyelonephritis as a result of obstruction by the ureteral tumor as well as the prostate.

Case 5.—G. O., Record No. 93893, a 64-year-old white female was admitted on April 29, 1946, because of progressive hematuria of one year's duration. For a number of years the patient had a dull ache just above the left iliac crest. The urinary stream seemed smaller in the past 6 months. There was some burning and occasional nocturia.

Physical examination was normal except for some induration of the right vaginal wall but none on the left. B.P. 135/70. Urinalysis disclosed 2 plus albuminuria, occasional granular casts, and many pus and red cells. Hb. 14 Gm.; rbc 4.0 million. Wbc 9,500; N 76 per cent, L 22 per cent, M 2 per cent. BUN 14.

Cystoscopy revealed a broad based papillary growth involving the entire right quadrant of the bladder but not the vesical neck. The ureteral orifices could not be seen. A flat plate of the abdomen disclosed a normal left kidney but the right was enlarged and seemed partially obscured by an associated soft tissue mass. Upon excretory urography, a normal left kidney was visualized but the right was non-functioning. A medium-sized lobulated mass of polypoid type occupied the right half of the bladder. Cholecystography demonstrated a normal gallbladder which was not connected with the right kidney.

On May 8 a suprapubic cystotomy was done. A cauliflower-like mass was attached to both the outside and inside of the right ureteral orifice. The mass was fulgurated. An elliptical incision was made around the orifice and the ureter freed. The growth was felt to end 2 inches above the orifice. The ureter was excised three quarters of an inch above the growth and re-implanted in the bladder.

Pathology report. "Gross: The specimen is a soft, cauliflowerlike piece of reddish-brown tissue. Microscopic: The tissue consists of arborizing papillae with slender vascularized stalks surmounted by moderately well-differentiated papillary transitional epithelium. Diagnosis: Moderately well differentiated papillary transitional cell carcinoma of ureter (Carcinoma, Grade II)."

The patient made an uneventful postoperative recovery. An excretory urogram on May 31 visualized a normal left kidney. Dye first appeared in 25 minutes on the right.

In 60 minutes a large right hydronephrosis and hydroureter were demonstrated. The bladder appeared normal. The patient was discharged from the hospital on June 3, 1946.

She was seen at two month intervals at the clinic. The patient remained well until October 25, 1946, when many pus cells with occasional red cells were found. Cystoscopy disclosed a normal bladder. Right kidney and bladder urine showed no pus cells and occasional red cells. Both specimens grew proteus organisms on culture. The last clinic visit of the patient was in January, 1947, at which time she felt well and had no complaints. In a telephone conversation in February, 1949, the patient stated that for the past month she had been losing weight, tired easily and was pale. However she did not wish to be cystoscoped.

Comment. Tumor seen protruding from an orifice is pathognomonic of carcinoma of the ureter or renal pelvis. Occasionally conservative surgery may be curative. It is always indicated where the involved kidney is necessary to sustain life.

Case 6.—A. M. S., Record No. 56355, a 64-year-old white male was admitted on July 1, 1948, because of hematuria. Four days prior to admission the patient had gross hematuria with the passage of clots. This cleared toward evening and recurred the following morning During the past week the patient had some difficulty in starting his stream and it was slightly diminished in size.

Positive physical findings were as follows: B.P. 165/95. The prostate was Grade I enlarged, soft and non-nodular. Urinalysis was negative except for 1 plus albuminuria. Hb. 16 Gm.; rbc 4.7 million. Wbc 8,500; N 64 per cent, E 5 per cent, B 1 per cent, L 27 per cent, M 2 per cent. BUN 24.

Cystoscopy demonstrated 4 ounces residual urine. The bladder mucosa was markedly trabeculated and the trigone congested. The posterior urethra was injected and bled easily. The lateral prostatic lobes were grade II in size with anterior notching, and moderate middle lobe enlargement. Indigocarmine appeared in 5 minutes from the right ureteral orifice but none in 15 minutes from the left. A 6F catheter passed 27 cm. with ease on the right. An obstruction was met at 15 cm. on the left which was passed with slight difficulty. Six cc. of radio-opaque medium filled the right pelvis and 14 cc. the left.

Retrograde pyelography disclosed a normal right kidney and ureter. There was marked hydronephrosis and hydroureter on the left. At the level of L4, a filling defect was seen in the ureter. The ureter below this defect appeared normal. A chest film showed no evidence of metastasis.

Cystoscopy was repeated on July 20. Bladder findings were the same. A catheter met an obstruction at 15 cm. which could not be passed. A diagnosis of left ureteral tumor was made.

On July 26 a left nephrectomy and partial ureterectomy were done. The ureter was twice normal size. At the junction of the middle and lower thirds, a small stonelike pebble was felt within the ureter. Immediately below this a soft mass was present. This portion of ureter had marked periureteritis. Below the mass the ureter was normal in size. The ureter was severed 1 inch below the mass.

Pathology report. "Gross: The kidney is hydronephrotic. An 8 cm. section of ureter exhibits a 2 by 1 cm. tumor 1 cm. from the distal end. Microscopic: Cross-section of the ureter shows the lumen to be almost completely occluded by an ingrowth from the lining. The neoplasm forms broad folds composed of layers of large, fairly sharply defined, irregularly shaped cells presenting numerous hyperchromatic nuclei and several atypical mitotic figures. A small lymphatic capillary in the ureteral wall is plugged with a mass of the malignant tumor. The kidney shows chronic inflammation. Diagnosis: Moderately

undifferentiated papillary transitional cell carcinoma of ureter with invasion of lymphatics (Papillary carcinoma Grade III); chronic pyelonephritis."

On August 1 a left ureterectomy, suprapubic prostatectomy and bilateral vasectomy were done. The ureter and a cuff of bladder surrounding it were removed. No enlarged lymph nodes were encountered in the dissection of the pelvis. The prostate was enucleated with ease.

Pathology report. "Gross: The ureter measures 4 cm. and displays one end which is mushroomed out by a mass of tough white tissue. The vasa are 2 thin brown coils of

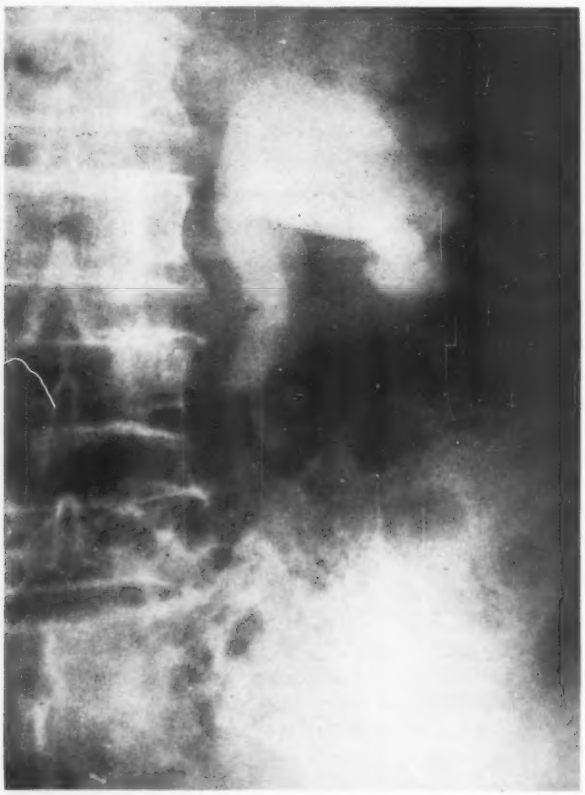


FIG. 1.—Case 6. Retrograde pyelogram showing filling defect in left ureter at L 4 with hydronephrosis and hydroureter above.

elastic tissue. The intact prostate weighs 18 Gm. Microscopic: Sections of ureter show slight ulceration of the lining, as well as lymphocytes and polys in the lumen and infiltrating the wall. The vasa are inflamed. Several sections of prostate gland show an intact, thick fibrous capsule encompassing hypertrophied lobules, exhibiting chronic inflammation. No evidence of malignant change is found. Diagnosis: Terminal portion of ureter, showing no residual tumor; portions of vasa deferentia; benign hypertrophy of prostate gland."

The patient was discharged on September 11, 1948. A course of deep roentgen ray therapy was advised and refused by the patient. He has been seen at the clinic at 2 month intervals and has continued in good health.

Comment. In all cases of hematuria, the upper as well as the lower urinary tract should be examined. Upon simple observation cystoscopy in this patient, it would have been concluded that he was bleeding from a congested hypertrophied prostate. A filling defect of the ureter is suggestive of tumor.

Case 7.—M. M., a 70-year-old white female, was admitted to the Graduate Hospital on August 14, 1948, with a chief complaint of hematuria. In May, 1947, the patient had an attack of left costovertebral pain accompanied by grossly bloody urine. A similar attack occurred in November, 1947. The patient first noticed a rapidly enlarging left abdominal mass in May, 1948. Two days prior to admission, there was a sudden onset of nausea, vomiting, and pain at the site of the mass.

Physical examination revealed the following: B.P. 150/90. A large, smooth, freely movable mass was present on the left side extending from the costal margin to the iliac crest. Urinalysis disclosed 3 plus albuminuria and many red cells. Hb. 50 per cent. BUN 70. An excretory urogram demonstrated a normal right and a non-functioning left kidney.

Three days later the patient's bladder became filled with clots and she went into left heart failure. The patient responded well to digitalis and a left nephrectomy was done on August 23. A large hydronephrotic kidney with complete atrophy of the renal tissue was found. The pathological diagnosis was: Hydronephrosis with destruction of kidney. The patient was discharged on September 13, 1948.

In January, 1949, painful lumps were noticed at the lower angle of the wound. A biopsy taken from this region was reported as transitional cell carcinoma. The patient was re-admitted to the hospital on February 6, 1949. Physical examination revealed a mass at the lower angle of the nephrectomy scar. There was some drainage from the site of the biopsy. Urinalysis disclosed 10 to 20 pus cells. Hb. 75 per cent; rbc 4.3 million. Wbc 11,300. BUN 15.

The patient had persistent gross hematuria. On February 26 a growth protruding from the left ureteral orifice was fulgurated cystoscopically. On March 11 an exploratory laparotomy was done. A mass extending from the bladder to above the bifurcation of the iliac vessels was found infiltrating the retroperitoneal wall. Biopsy was reported as transitional cell carcinoma. Review of the previous kidney specimens showed no evidence of tumor. The patient is now receiving deep roentgen ray therapy.

Comment. When a mass is palpable in carcinoma of the ureter, it is usually that of a hydronephrotic kidney. This case had all three of the textbook triad of hematuria, pain and mass. In all cases of "non-functioning kidney" upon excretory urography, retrograde pyelo-ureterography should be done.

DISCUSSION

Diagnosis. Hematuria is the most prominent symptom, occurring in 70 to 75 per cent of the cases. It may be the only symptom or may be entirely absent. It is usually profuse, intermittent and painless. Occasionally it disappears in a few days under symptomatic treatment, not to recur for several months. Pain is the second most common symptom, occurring in 60 per cent of the cases. Lazarus and Marks,[13] in a review of 108 cases, found that 71 had renal pain, nine abdominal pain, and 28 simple backache. The pain is usually dull and dragging, secondary to the hydronephrosis. Colic may result from the passage of blood clots or superimposed calculus. Pain may arise from pressure or from invasion of adjacent structures. Israel has reported sciatica

due to pressure on the sacral plexus. Of the textbook triad, pain, hematuria and mass, the last is least common, being found in about 45 per cent of the cases. The mass palpated is usually the hydronephrotic kidney. Only rarely, as in the case of a well developed tumor, can the actual carcinoma be felt. Butler,[2] and Paschkis and Pleschner[16] have reported palpation of these tumors rectally and vaginally.

According to Edelstein and Marcus,[4] urinary frequency occasionally occurs, especially if the tumor is in the lower third of the ureter, which was the case in 60 per cent of those reported by Vest. The hydronephrotic kidney may become secondarily infected, leading to symptoms of pyelonephritis, acute or chronic, pyonephrosis, or perinephric abscess.

Scott states that the correct preoperative diagnosis is made in less than 36 per cent of the cases. In approximately 30 per cent, blood can be seen coming from the ureteral orifice of the involved side. Papillary excrescences protrude from the orifice in 25 to 30 per cent of the cases. Ureteral obstruction upon catheterization is present in 50 to 60 per cent. Bleeding may follow manipulation of the catheter. Especially significant is obstruction to the passage of a catheter which occasions fresh bleeding followed by clear urine after the catheter has passed the obstruction.

The preoperative diagnosis has most often been made by the presence of a filling defect in the pyelo-ureterogram. This is not always successful where the tumor prevents the radio-opaque medium from ascending. Neuwirth and Bedrna[15] demonstrated the value of pneumo-pyeloureterography in these cases. Vest[20] states that a filling defect in roentgen ray occurs in only 15 per cent of cases. According to Kimball and Ferris,[11] it is important to remember that these ureteral tumors may arise from tumors of the renal pelvis.

Carcinoma may sometimes be diagnosed by the presence of exfoliated tumor cells in urine.

In Lazarus and Marks[13] review, men were affected twice as frequently as women. The greatest incidence occurred in the fifth to sixth decade, although the range in Scott's[19] series was from ages of 22 years to 89. The right ureter was involved over the left in a ratio of 3 to 2. In differential diagnosis, tumors of the kidney, bladder and prostate, tuberculosis, calculi, and ureteral stricture must be considered.

Treatment. The most acceptable form of treatment, according to the literature, is an extraperitoneal nephro-ureterectomy with removal of a cuff of bladder. Excision of the tumor bearing area in the lower ureter with reimplantation of the ureter into the bladder is the commonest conservative procedure. Vest advocates the local removal of the ureteral tumor in those cases which are clinically and histologically believed to be benign, and in which loss of function of the involved side would prove immediately fatal. Deep roentgen-ray therapy has proved to be of little value so far as cure is concerned.

Most of the patients reported in the literature die within two years after operation. Because the ureter has a thin wall and an abundant blood and

lymphatic supply, metastases occur early. The commonest sites are in the retroperitoneal lymph nodes 30 per cent, liver 14 per cent, bones 12 per cent, lungs 5 per cent, and bladder 6 per cent.

Pathology. In his review of 182 cases, Scott[19] lists 22 categories into which these tumors have been placed. Since the pathological characteristics of all tumors of the urinary transitional epithelium (Melicow's urothelium) are similar, the grading system of the Registry of Bladder Tumors[8] should be employed here. According to this system, Grade I comprises the papillomata with typical cells and no invasion of bladder or pedicle. Grade II includes tumors which are not uniform in cell arrangement or type and in which there may or may not be histologic evidence of invasion. Grade III are tumors showing infiltration, cellular atypism and considerable mitotic activity. Extremely anaplastic tumors are placed in Grade IV.

Most authors are inclined to regard all epithelial tumors of the genitourinary tract as at least potentially malignant, although Vest[20] has collected a series of benign ureteral tumors. The Registry's experience with Grade I lesions of the bladder seems to be in agreement with this concept for such tumors have often progressed to frank carcinoma.

Due to the difficulty of diagnosis and the consequent delay of treatment, ureteral tumors often progress farther than those of the bladder. Behavior of all tumors of the urinary tract is extremely difficult to predict. In general, infiltrating tumors lead to earlier metastasis than non-infiltrating, although Grade I tumors may unexpectedly metastasize.

The cause of tumors of the urinary transitional epithelium is not known. It seems inescapable that some component of the blood or urine is at least partly responsible. Pearse's[17] cases in which marked regression of bladder tumors followed ureteral transplants would seem to indict the urine, although Gay[7] and Ferguson[6] have favored a blood-borne agent.

There are certain circumstances which undoubtedly predispose to carcinoma. The outstanding instance is that of chronic exposure to aniline dyes either in industry or experiment. Willis[22] believes that exstrophy of the bladder predisposes to carcinoma and that schistosomiasis might. He also believes that Brunn's nests and other forms of metaplasia predispose to adenocarcinoma. Bothe[1] found such changes in areas near ureteral tumors and thought that they were the precursors of frank tumor. Fagerstrom[5] could find no correlation between epithelial budding and solid tumors of urinary epithelium. The question of chronic infection predisposing to carcinoma is difficult to assess and the recent literature does not emphasize it. Willis[22] says that the first symptoms of bladder carcinoma are due to the tumor rather than other urinary disease.

SUMMARY

Seven cases of primary carcinoma of the ureter are reported. Hematuria, pain and mass, in that order, are the most common symptoms. The mass is usually a hydronephrosis secondary to obstruction by the tumor. Symptoms

may result from an infected hydronephrosis. Tumor seen protruding from a ureteral orifice is pathognomonic of carcinoma of the ureter or renal pelvis. A filling defect in the pyelo-ureterography is suggestive. Treatment should be radical. Conservative surgery is indicated where the involved kidney is necessary to sustain life. Most of these patients die within two years after the diagnosis has been made. A plea is made to follow the Registry of Bladder Tumors classification. The cause of these tumors is unknown. All are potentially malignant.

We wish to thank Dr. Joseph C. Birdsall and Dr. Ernest G. Williamson for permission to include their cases in this paper. We express our appreciation for the aid Dr. R. Philip Custer gave us in the preparation of portions of this paper.

BIBLIOGRAPHY

1 Bothe, A. E.: J. Urol., **53**: 451, 1945.
2 Butler, F. A.: Clifton Med. Bull., **2**: 46, 1914.
3 Chute, R., and D. W. Williams: J. Urol., **59**: 604, 1948.
4 Edelstein, J. M., and S. M. Marcus: J. Urol., **60**: 409, 1948.
5 Fagerstrom, D. P.: J. Urol., **59**: 333, 1948.
6 Ferguson, R. S.: J. Urol., **38**: 243, 1937.
7 Gay, D. M.: J. Urol., **38**: 221, 1937.
8 Grading of Epithelial Tumors of the Urinary Bladder. J. Urol., **36**: 651, 1936.
9 Gualtieri, T., J. J. Hayes and A. D. Segal: J. Urol., **59**: 1083, 1948.
10 Israel, J.: Berlin klin. Wchnschr., **47**: 2381, 1910.
11 Kimball, F. N., and H. W. Ferris: J. Urol., **31**: 257, 1934.
12 Lazarus, J. A.: Ann. Surg., **99**: 769, 1934.
13 Lazarus, J. A., and M. S. Marks: J. Urol., **54**: 140, 1945.
14 Melicow, M. M.: J. Urol., **54**: 186, 1945.
15 Neuwirth and Bedrna: Casopis Lekaru Ceskych., **67**: 47, 1928.
16 Paschkis, R., and H. Pleschner: Med. Klin., **16**: 1254, 1920.
17 Pearse, R.: Discussion. J. Urol., **49**: 32, 1943.
18 Sauer, H. R.: J. Urol., **48**: 467, 1942.
19 Scott, W. W.: J. Urol., **50**: 45, 1943.
20 Vest, S. A.: J. Urol., **53**: 97, 1945.
21 von Brunn, A.: Arch. f. mikr. Anat., **41**: 294, 1893.
22 Willis, R. A.: Pathology of Tumors, pp. 468–480, 1948, St. Louis, C. V. Mosby Co.

ADDENDUM—THREE LATE CASES

Case 8.—E. F. S., No. 107668. Right nephrectomy was done in 1947 because of hydronephrosis; re-admitted February, 1949, with burning and frequency. Cystoscopy revealed a papillary tumor surrounding R. U. O. Right ureterectomy including bladder cuff was done, with discharge April 19, 1949.

Pathology Report. Transitional cell carcinoma, grade two, of the ureter.

Case 9.—R. E. A., No. 21705. Admitted June, 1949, with hematuria nine months. Papilloma near left ureteral orifice fulgurated September, 1948. Several recurrences fulgurated. Left ureteronephrectomy was done, with excellent recovery.

Pathology Report. Papillary transitional cell carcinoma, grade two, of ureter.

Case 10.—A. B. Hematuria ten days. The tumor, protruding from the ureteral orifice, fulgurated elsewhere a week before. Excretory urogram revealed a lesion of the distal end of the right ureter. Nephroureterectomy was done, with recovery.

Pathology Report. Transitional cell carcinoma, partially differentiated, of the right ureter.

ANEURYSM OF THE COMMON CAROTID ARTERY*

CHARLES K. KIRBY, M.D., JULIAN JOHNSON, M.D.,
AND JAMES G. DONALD, M.D.

PHILADELPHIA, PA.

FROM THE SURGICAL CLINIC OF THE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA AND THE HARRISON DEPARTMENT OF SURGICAL RESEARCH, SCHOOLS OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA

Aneurysm of the common carotid artery is a relatively uncommon lesion. During a 20-year period, from 1927 to 1947, this diagnosis was made only five times in the surgical service of the Hospital of the University of Pennsylvania. In Reid's review[1] of aneurysms treated at the Johns Hopkins Hospital only ten were found to involve the common carotid artery. In occasional reports during the past 15 years this lesion has been discussed and cases have been added to the literature.[2-7] This is in contrast to aneurysm of the internal carotid artery which is relatively common.

At least 90 per cent of all aneurysms of the common carotid artery are due to syphilis.[8] Hence, as this disease becomes more uncommon, this aneurysm will become increasingly rare. Most spontaneous aneurysms of the internal carotid artery, on the other hand, are now generally conceded to be congenital in origin.[9] Traumatic aneurysms are usually due to gunshot wounds or stab wounds.

The treatment of common carotid aneurysms, particularly of spontaneous aneurysms, has been difficult and often disappointing. Reid[1] considered that only four of the ten reported by him were known to be cured. In using treatment radical enough to effect a cure, hemiplegia has been a constant threat. Recurrence has frequently followed the use of conservative methods, such as simple ligation. In some instances hemiplegia has occurred hours or days following an operation thought, at first, to be successful. Hemorrhage resulting from the erosion of bands or ligatures has been a serious complication. In general, six types of management have been recommended:

1. Do nothing. Some have considered the prognosis to be better without surgical treatment, particularly in patients over 50 years of age.
2. Proximal occlusion of the common carotid artery, with bands or ligatures.
3. Distal occlusion of the common or of the external and internal carotid arteries.
4. Proximal and distal occlusion, simultaneously or in stages.
5. Aneurysmorrhaphy, using any of the three classical methods of Matas.
6. Excision, following proximal and distal ligation.

Small aneurysms have been cured by methods 2, 3, and 4, but these methods have not been successful in curing large aneurysms, even though pulsations were at first obliterated. The fifth method, aneurysmorrhaphy, has been applicable and successful for some traumatic aneurysms but has been

* Submitted for publication March, 1949.

infrequently used for spontaneous aneurysms because of the difficulty of suturing vessel walls, the site of advanced degenerative disease. Excision, when not followed by complications, has given excellent results and has been curative.

The major problem in treating these lesions has been the danger of hemiplegia resulting from ligation of the carotid arteries. The incidence of cerebral complications following carotid ligation cannot be stated with certainty because of the many variable factors involved. Pilcher and Thuss,[10] in an extensive review of the world literature, concluded that cerebral complications occur in 20 to 30 per cent. Watson and Silverstone[11] reported cerebral complications in 70 per cent and a mortality of 50 per cent following carotid ligations in patients with cancer of the head and neck. These figures are probably higher than average because of the age and debility of many of their patients. Freeman[12] reported cerebral complications in 20 to 25 per cent and Matas[13] a mortality of 12 per cent following ligation of the common carotid artery. Lahey and Warren[14] considered the risk of carotid ligation too great to be warranted during excision of carotid body tumors.

Various methods of testing and of increasing the adequacy of collateral circulation have been proposed to reduce the incidence of cerebral complications. These have been discussed by Matas,[15] Dandy,[16] Schorstein,[17] Olivecrona,[18] Dorrance,[19] Jefferson,[20] Sweet and Bennett,[21] and others. The methods commonly used have been:

1. External application of pressure preoperatively. Occlusion of the carotid artery with the finger (Matas test) has been generally considered a reliable test of the collateral circulation. In case of doubt, attempts have been made to increase collateral circulation by the application of pressure intermittently, with the finger or with the compression caliper clamp of Matas. Although this is undoubtedly a helpful method, certain limitations cannot be disregarded:

   a. Stimulation of the carotid sinus may cause syncope and other cerebral symptoms, with resultant confusion in the interpretation of the test.

   b. Sudden occlusion of a carotid artery may cause hemiplegia.[22]

   c. The test is not always reliable, hemiplegia sometimes following carotid ligation when adequate collateral circulation appears to be present.[14, 18]

   d. It is difficult to be certain that the carotid artery is completely occluded by digital pressure, as demonstrated in the recent experiments of Sweet and Bennett.[21]

2. Occlusion of the carotid artery, exposed under local anesthesia for 30 minutes or more. This variation of the Matas test has been used to eliminate any doubt that the artery is completely occluded. Hemiplegia has followed hours or days later in some in whom this test was negative. Dandy[16] believed that a propagating thrombus or an embolus accounted for such a complication, while Schorstein[17] presented evidence that it may be due to the delayed effects of ischemia, present at the time of ligation, but not becoming clinically apparent except as a result of a prolonged, cumulative effect.

3. Partial occlusion by constricting metal or fascial bands for one to six weeks to promote the development of adequate collateral circulation. This method was used particularly by Dandy,[9] who considered it a satisfactory solution to the problem because of the rapid development of collateral circulation in response to this stimulus. In Dandy's experience it was rarely necessary to remove a band if care was taken to produce no more than 50 per cent occlusion of the artery, and excellent protection was afforded to the patient when ligation was finally performed. Dandy emphasized that the development of collateral circulation was unlikely in some individuals because of the presence of congenital anomalies of the Circle of Willis. These individuals could be eliminated, he believed, by the development of cerebral symptoms within ten minutes following digital occlusion of the carotid artery.

4. Active bleeding from the distal end of the vessel. This is an old method, used frequently by Halsted.[1] Actual spurting from the distal end of the artery has proved to be reliable evidence that the collateral circulation is adequate.

Using a sensitive manometer, Sweet and Bennett[21] have recently studied the collateral circulation of the carotid arteries by measuring the pressure in the internal carotid artery during occlusion of the common carotid, common and external carotid, and both common carotid arteries. Their results have led them to propose this procedure as a method for testing the adequacy of the collateral circulation. In patients who withstood common carotid occlusion well the systolic pressure fell to 50 per cent and the pulse pressure to 25 per cent of its original level, demonstrating that carotid ligation for intracranial aneurysm reduces intra-aneurysmal pressure and, presumably, aids in thrombus formation. This technic was used to test the thesis that ligation of the common carotid is safer than ligation of the internal carotid artery, as contended by Dorrance,[19] Schorstein,[17] and Olivecrona,[18] because of collateral circulation passing from the opposite carotid artery through the external and into the internal carotid artery of the same side. The pressure recordings indicated that significant retrograde flow from the external to the internal carotid artery did not occur when the common carotid artery only was occluded. They concluded that, in elective procedures, the internal carotid should be ligated, as practiced by Dandy,[9] rather than the common carotid artery. Finally, there was no evidence in their studies that the circulation was improved, following occlusion of the carotid arteries, by simultaneous occlusion of the internal jugular vein.

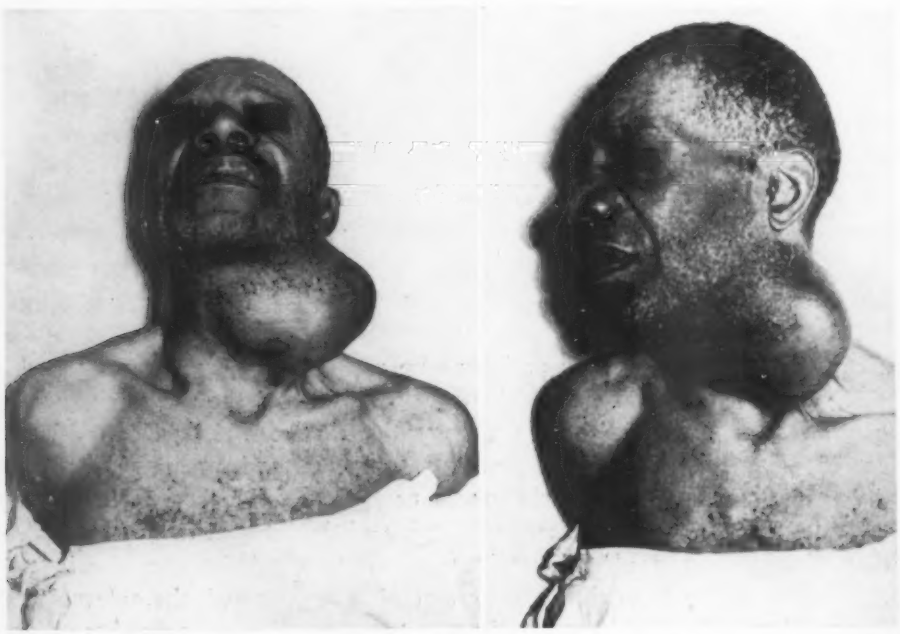
An unusually large luetic aneurysm of the common carotid artery was recently treated successfully at the Hospital of the University of Pennsylvania by excision. Preoperatively it was planned to use a vein or arterial graft if the collateral circulation appeared inadequate.

CASE REPORT

A. M., a 61-year-old man, was admitted to the Hospital of the University of Pennsylvania on April 30, 1948. In November, 1946, he noted a pulsatile swelling on the

left side of the neck, just above the clavicle. Several months later a similar but smaller lump appeared on the right side of the neck. The lesion on the left increased gradually in size but that on the right did not. In January, 1948, the lump on the left, which was about the size of on orange, began to grow rapidly in size. Hoarseness, severe constant pain, and difficulty in swallowing developed. During the four months prior to admission he lost 40 pounds in weight.

Physical Examination: The patient was apparently in great pain, with a large pulsating mass on the left side of the neck (Fig. 1). The trachea was displaced far to the right. Just above the right clavicle there was a pulsating tumor 2.5 cm. in diameter. The left vocal cord was paralyzed. The blood pressure was 200/110 in both arms. The heart was moderately enlarged, and there was a soft, blowing diastolic murmur heard along the left border of the sternum. The peripheral arteries were sclerotic and tortuous.



A B

FIG. 1.—Photographs taken on admission, showing the size of the aneurysm of the left common carotid artery. The small aneurysm of the right common carotid artery is shown in (A).

A neurologic examination revealed no evidence of central nervous system syphilis. There were no other positive findings.

Laboratory Tests: A complete blood count, urinalysis, blood urea nitrogen, carbon dioxide combining power, serum protein and chloride were within normal limits. A blood Kolmer, Kline, and Wassermann were positive.

Chest Roentgenogram: There was moderate cardiac enlargement, particularly to the left, and moderate dilatation of the aortic arch.

Roentgenogram of the Tibiae: There was thickening of the cortex and anterior bowing, consistent with a diagnosis of syphilitic osteitis.

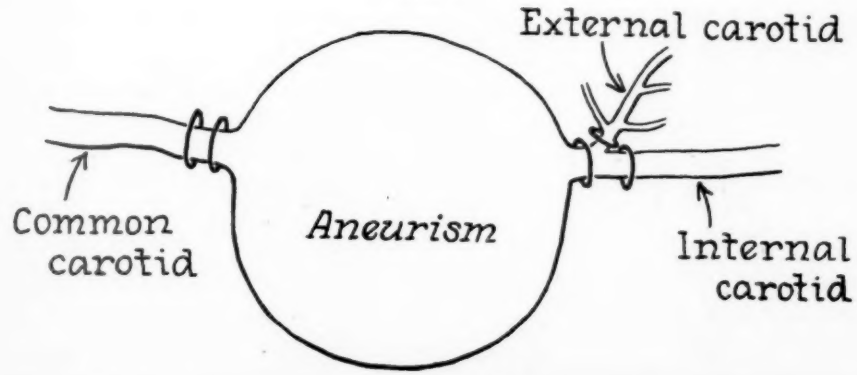
Electrocardiogram: Normal except for left axis deviation.

Clinical Course: The patient was in constant pain and was unable to eat. Rupture of the aneurysm appeared imminent. A successful surgical attack on this lesion was obviously the only means of prolonging his life. Compression of the left common carotid

artery just above the clavicle stopped the pulsations of the aneurysm and caused no apparent cerebral symptoms. Digital pressure could not be tolerated for more than 10 minutes because of pain.

Operation: Performed May 3, 1948, with endotracheal cyclopropane anesthesia Transverse incisions three inches long were made just above and below the aneurysm, and a vertical incision was made between the midpoints of the transverse incisions. Subplatysmal flaps were reflected. Hernia tapes were passed around the common carotid artery proximal and distal to the aneurysm, which was found to be fusiform in type (Fig.

FIG. 2



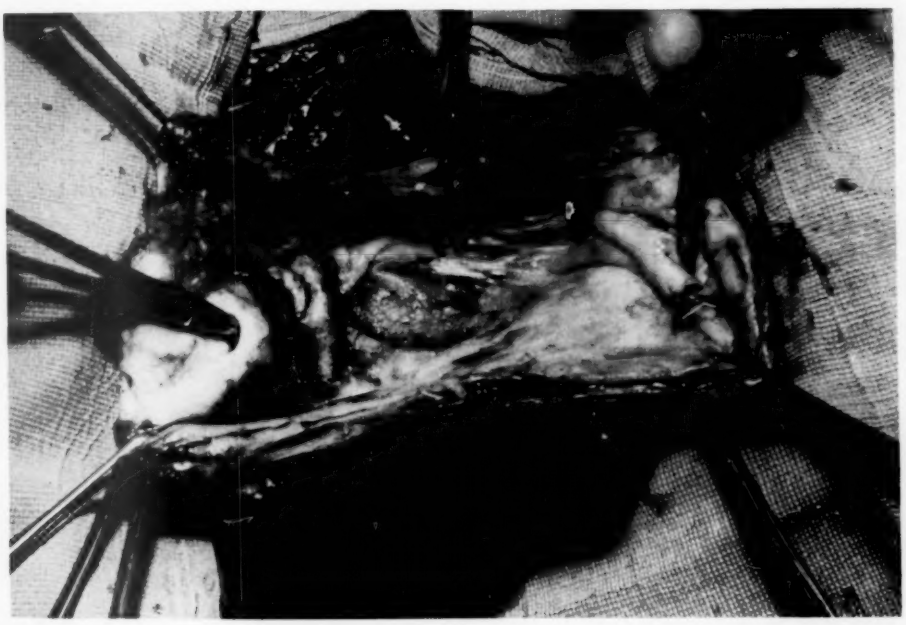


FIG. 3

FIG. 2.—The configuration of the aneurysm and the points of ligation are shown diagrammatically.

FIG. 3.—A photograph taken at operation just after the sac was opened. Kelly clamps have been inserted into the common carotid artery proximal and distal to the aneurysm.

2). Adjacent structures, which were densely adherent to the wall of the aneurysm, were freed by sharp dissection. The left internal jugular vein and vagus nerve lost their identity in dense, matted scar tissue medial to the lesion. The dissection proceeded without difficulty except at a point on the lateral wall of the pharynx where the aneurysmal sac and pharynx were entered simultaneously. At this point only a thin layer of pharyngeal wall and aneurysmal sac remained as a barrier against rupture. The opening in the pharynx, about one-half inch in length, was closed with chromic catgut sutures. The aneurysm was then opened widely (Fig. 3), and the dissection was completed. With noncrushing clamps applied to the artery proximally and distally, the sac was excised.

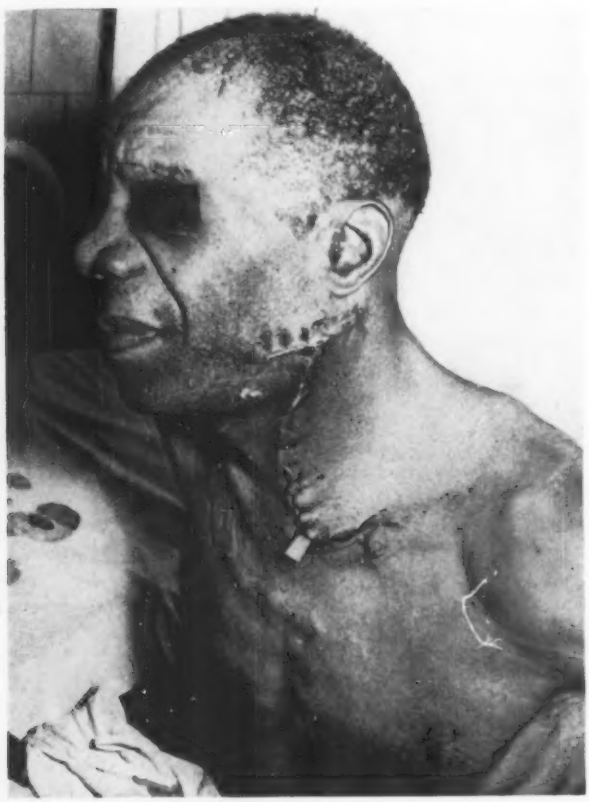


FIG. 4.—A photograph on the first postoperative day.

Preparations had previously been made to use an arterial graft from a fresh cadaver. Because of advanced degenerative changes, the patient's carotid artery was tested with sutures. These were found to cut through easily. Because of this it was thought safer to avoid a graft if the collateral circulation could be shown to be adequate. This was tested in two ways. First, the clamp was removed from the distal end of the artery. The blood spurted, under strong pressure, for a distance of at least three feet. Second, anesthesia was stopped and the patient was permitted to wake up. It was found that the upper and lower extremity on the contralateral (right) side could be moved freely. With this evidence of adequate collateral circulation and the uncertainty of the suture-holding ability of the patient's vessel, ligation was considered preferable to a grafting procedure. Heavy silk ligatures were applied to the common carotid artery proximally

and to the common, internal and external carotid arteries distally. The wound was closed with one dependent drain, which was removed on the first postoperative day (Fig. 4). A tracheotomy was performed 36 hours after operation because of excessive tracheobronchial secretions with dyspnea and apparent respiratory obstruction. The patient was digitalized because of auricular fibrillation. There was no evidence at any time of cerebral ischemia or neurologic sequelae. The tracheotomy tube was removed after two weeks, and the patient was discharged on the 26th postoperative day. When last seen, eight months after operation, he had regained his normal weight and appeared well. The aneurysm of the right common carotid artery had become no larger.

COMMENT

In this elderly patient the use of three simple tests demonstrated that adequate collateral circulation had developed. Cerebral disturbances did not occur during carotid occlusion preoperatively; retrograde bleeding was in strong spurts when the distal clamp was removed during operation, and there was normal motor function on the contralateral side of the body following carotid occlusion during operation. It is not likely that such evidence of adequate collateral circulation will always signify freedom from cerebral complications in view of the late sequelae reported by Dandy[16] and Schorstein.[17] The use of carotid intra-arterial pressure recordings during operation, suggested by Sweet and Bennett,[21] may prove to be a useful refinement in evaluating collateral circulation. Although the equipment used by them was considered too complicated for routine use, a simpler and more compact instrument, such as that of Peterson, Dripps, and Risman,[23] in use in the operating rooms of the Hospital of the University of Pennsylvania, may be satisfactory.

Our experience with vein grafts in experimental animals and in patients,[24] and the experience of Gross[25] with artery grafts demonstrate that defects of large arteries can be satisfactorily bridged by grafting procedures. In elderly patients one is confronted with the problem of suturing a healthy graft to friable, arteriosclerotic vessels. The reliability of the suture method of anastomosis under such circumstances has not been established. The type of suture used may be a factor of importance. In an arteriosclerotic patient in whom Lexer[26] replaced a femoral artery aneurysm with a saphenous vein graft a Carrel suture cut through the friable arterial wall whereas a continuous everting mattress suture was entirely satisfactory. In patients with degenerative changes in the arterial walls the nonsuture method of Blakemore and Lord[27, 28] may be useful.

SUMMARY

1. The problems of treatment of aneurysms of the common carotid artery and of ligation of the carotid arteries have been briefly discussed.

2. An instance of successful excision of an unusually large luetic aneurysm of the common carotid artery in an elderly patient has been described.

BIBLIOGRAPHY

[1] Reid, M. R.: Aneurysms in the Johns Hopkins Hospital: All Cases Treated in the Surgical Service from the Opening of the Hospital to January, 1922. Arch. Surg., 12: 1, 1926.

2 Elkin, D. C., and J. L. Campbell: Aneurysm: A Review of Sixty-two Cases. Am. J. Surg., **24**: 611, 1934.

3 Matas, R.: Classified Summary of 620 Operations on the Blood Vessels for All Causes. Tr. Am. S. A., **58**: 335, 1940.

4 Rossello, G.: Spontaneous Aneurysm of Right Common Carotid Artery: Ligation of Internal and External Carotids Followed by Grave Cerebral Alteration; A Case in a Patient with Syphilitic Arteritis. Arch. ital. di. chir., **54**: 316, 1938.

5 Pataro, V.: Carotid Aneurysm with Ligature. Prensa med. argent., **30**: 2024, 1943.

6 Collins, F. M.: Aneurysm (Syphilitic) of Common Carotid Bifurcation Treated by Double Proximal and Distal Ligature. J. Roy. Army M. Corps, **84**: 278, 1945.

7 Whalley, N.: Traumatic Aneurysm of the Common Carotid Artery Associated with Massive Infarction of the Brain. British J. Surg., **33**: 400, 1946.

8 McNealy, R. W.: Aneurysms. Lewis' Practice of Surgery. Vol. XII. W. F. Prior Co., Inc., Hagerstown, Md., 1948.

9 Dandy, W. E.: Results Following Bands and Ligatures on the Human Internal Carotid Artery. Ann. Surg., **123**: 384, 1946.

10 Pilcher, C., and C. Thuss: Cerebral Blood Flow: III. Cerebral Effects of Occlusion of the Common or Internal Carotid Arteries. Arch. Surg., **29**: 1024, 1934.

11 Watson, W. L., and S. M. Silverstone: Ligature of the Common Carotid Artery in Cancer of the Head and Neck. Ann. Surg., **109**: 1, 1939.

12 Freeman, L.: The Causation and Avoidance of Cerebral Disturbances in Ligation of the Common Carotid Artery. Ann. Surg., **74**: 316, 1921.

13 Matas, R., Quoted by W. E. Dandy: Intracranial Arterial Aneurysms (VIII), Comstock Publishing Co., Inc., Ithaca, N. Y., 1944.

14 Lahey, F. H., and K. W. Warren: Tumors of the Carotid Body. Surg., Gynec. & Obst., **85**: 281, 1947.

15 Matas, R.: Discussion on Papers of Drs. Elkin and Campbell, Dr. Matas and Dr. Gage. Am. J. Surg., **24**: 692, 1934.

16 Dandy, W. E.: Intracranial Arterial Aneurysms (VIII), Comstock Publishing Co., Inc., Ithaca, N. Y., 1944.

17 Schorstein, J.: Carotid Ligation in Saccular Intracranial Aneurysms. Brit. J. Surg., **28**: 50, 1940.

18 Olivecrona, H.: Ligature of the Carotid Artery in Intracranial Aneurysms. Acta chir., scandinav., **91**: 353, 1944.

19 Dorrance, G. M.: Ligation of the Great Vessels of the Neck. Ann. Surg., **99**: 721, 1934.

20 Jefferson, G.: On the Saccular Aneurysms of the Internal Carotid Artery in the Cavernous Sinus. Brit. J. Surg., **26**: 262, 1938.

21 Sweet, W. H., and H. S. Bennett: Changes in Internal Carotid Pressure During Carotid and Jugular Occlusion and Their Clinical Significance. J. Neurosurg., **5**: 178, 1948.

22 Kay, C. F.: Personal communication.

23 Peterson, L. H., R. D. Dripps and G. Risman: A Method for Recording the Arterial Pressure, Pulse and Blood Pressure in Man. Am. Heart J. (in press).

24 Johnson, J., and C. K. Kirby: Experimental and Clinical Use of Vein Grafts to Replace Defects in Large Arteries. To be published.

25 Gross, R. E., E. S. Hurwitt, A. H. Bill and E. C. Pierce: Preliminary Observations on the Use of Human Arterial Grafts in the Treatment of Certain Cardiovascular Defects. New England M. J., **239**: 578, 1948.

26 Lexer: Cited in Berlin News Letter. J. A. M. A., **60**: 1474, 1913.

27 Blakemore, A. H., and J. W. Lord: A Nonsuture Method of Blood Vessel Anastomosis. Review of Experimental Study: Report of Clinical Cases. Ann. Surg., **121**: 435, 1945.

28 Blakemore, A. H.: Restorative Endoaneurysmorrhaphy by Vein Graft Inlay. Tr. Am. S. A., **65**: 46, 1947.

POSTOPERATIVE DIABETES MELLITUS FOLLOWING RESECTION OF THE BODY AND TAIL OF THE PANCREAS FOR SECONDARY INVASION BY GASTRIC CANCER*

ALEXANDER BRUNSCHWIG, M.D.
AND
FERNANDO GENTIL, M.D.
NEW YORK, N. Y.

FROM THE MEMORIAL HOSPITAL FOR THE TREATMENT OF CANCER AND ALLIED DISEASES
NEW YORK CITY

RECENT ADVANCES in the surgery of the pancreas have afforded interesting observations upon the physiology of this organ in man. For example, it has been found that the external pancreatic secretion is not essential to the maintenance of a normal nutritional status in some instances.[1] It has also been observed that the totally depancreatized human being presents only a relatively mild diabetes that is less severe than many instances of spontaneous diabetes in individuals with the entire pancreas in situ. More surprising is the fact that total pancreatectomy in the diabetic human has not resulted in augmentation of the severity of the diabetes already present.[2]

In previous experiences the head of the pancreas seemed to represent adequate tissue to permit normal carbohydrate metabolism, since in a number of instances where the body and tail of the organ were resected because of secondary invasion by neoplasm arising in an adjacent organ, postoperative diabetes did not develop. However, in the past several months three patients from the private service of one of us (A.B.) had the body and tail of the pancreas resected incident to total gastrectomy for gastric carcinoma and developed transitory postoperative diabetes for which insulin was administered. The case histories are summarized below:

Case 1.—I. B., a 57-year-old white housewife, first seen at Memorial Hospital on October 29, 1947, at which time she gave the following history: In June, 1938, the patient was submitted to a gastric resection, apparently for a small neoplasm of the stomach. Six months prior to the operation the patient developed epigastric discomfort associated with belching and slight weight loss. Subsequent to the operation the patient felt well, gained weight and had no complaints until the early fall of 1947, at which time the symptoms recurred—epigastric discomfort, weight loss and an increasing difficulty in swallowing solid foods. The patient was thoroughly studied and a diagnosis of recurring gastric carcinoma was made based upon roentgenographic appearance of the remaining stomach; the walls of this segment were quite rigid.

Physical examination at the time of admission to the Memorial Hospital showed a well-developed white female presenting signs of moderate weight loss but not in acute discomfort. Abdomen showed a well-healed midline scar and on palpation there was a definite epigastric fullness which was slightly tender. The liver was not enlarged; spleen and kidneys not palpated. Pelvic examination revealed no metastatic masses.

Preoperative laboratory studies: (1) Blood chemistry: serum protein 5.5 Gm. per 100 cc.; blood urea nitrogen 15.0 mg. per 100 cc.; blood sugar analysis not done.

* Submitted for publication February, 1949.

(2) Blood: Hemoglobin 78 per cent; white cells 8.3. (3) Urinalysis: specific gravity 1.022, reaction acid, color amber, *negative for albumen and sugar.* (4) Chest film: negative for metastases.

Operation November 1, 1947. The findings were as follows: The remainder of the stomach (the patient had had a previous gastrectomy) was involved in a large neoplastic process. The previous gastro-intestinal anastomosis was obviously invaded by the tumor; the remaining gastro-hepatic ligament was short and grossly free of disease. In the

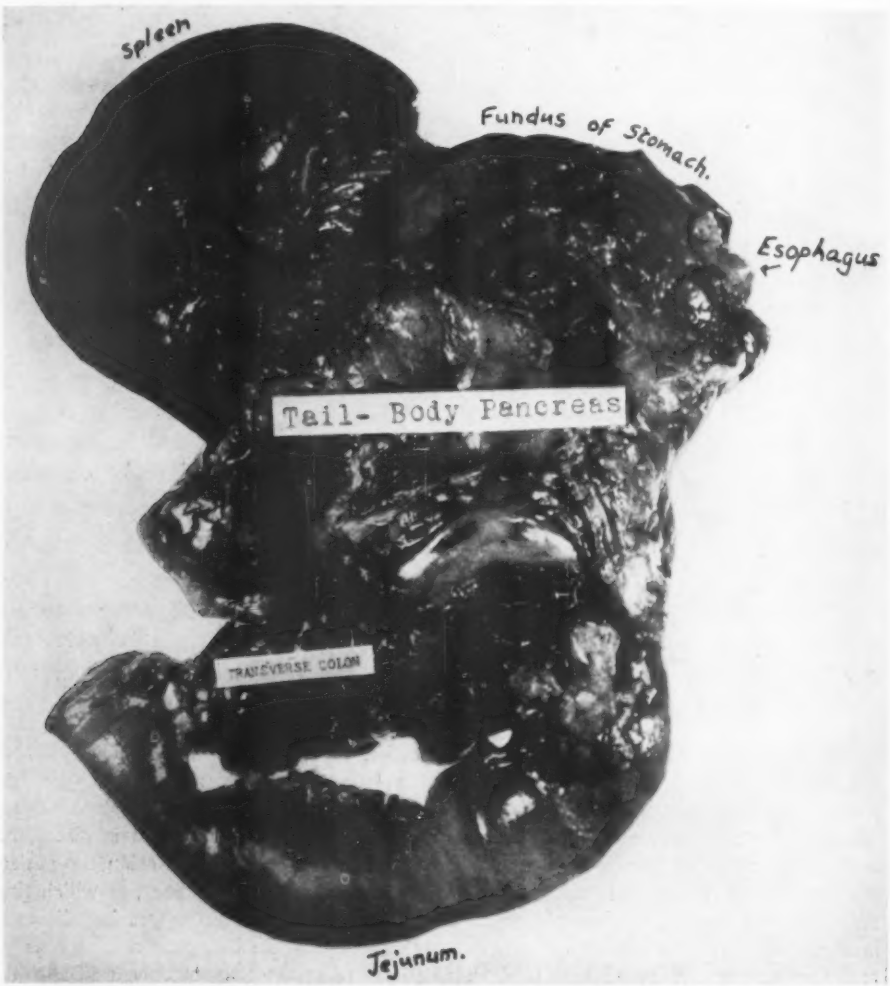
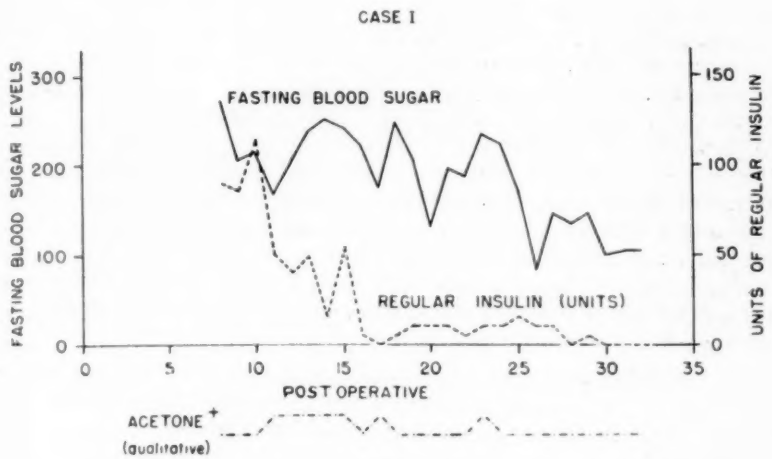


FIG. 1.—(Case 1). Photograph of posterior view of operative specimen consisting of residual upper third of stomach involved in recurrent carcinoma (a radical gastrectomy had been performed ten years previously for carcinoma). The spleen and entire body and tail of pancreas were resected also, as well as the loop of jejunum brought up for gastro-jejunostomy at the previous operation. Mid-portion of transverse colon is not well shown in the photograph and was also removed.

mesocolon two metastatic nodules were found. The tumor was firmly adherent to the body of the pancreas. The liver was free from metastases but contained a small mass located on the lower border of its right lobe which was bluish in color and grossly

resembled a hemangioma. The remaining stomach, spleen, body and tail of pancreas and transverse colon were resected en masse. Resection of hemangioma of liver was performed. The alimentary tract was reconstituted by esophago-jejunostomy, entero-enterostomy, and colocolostomy (end-to-end). A photograph of the specimen is shown in Fig. 1. The patient withstood the procedure satisfactorily and received 2,000 cc. of blood and 1,000 cc. of 5 per cent dextrose in distilled water during the operation.

FIG. 2



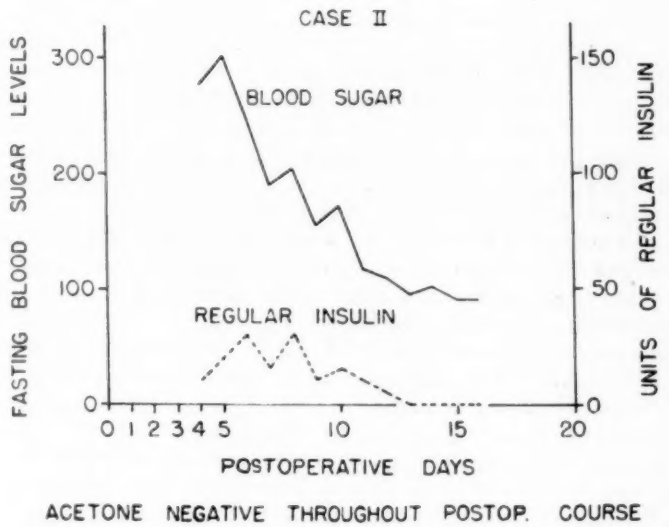


FIG. 3

FIG. 2.—(Case 1) Graph showing levels of morning fasting blood sugar observed after the eighth postoperative day. The postoperative diabetic state lasted until the twenty-sixth postoperative day after which it was very mild. Daily insulin intake is also shown.

FIG. 3.—(Case 2.) Graph showing fasting morning blood sugar levels observed daily after the 4th postoperative day. The postoperative diabetic state lasted until about the thirteenth day. Daily doses of insulin also indicated.

Pathologic report: "Signet-ring adenocarcinoma, Grade IV., with extension to gastrocolic ligament, peri-pancreatic fat, mesentery and nodes. The line of esophageal resection was involved along with the esophageal node, and there was cavernous hemangioma of the liver."

Postoperative course: The immediate postoperative course was uneventful but by the ninth day physical signs and drainage from the upper part of the wound indicated the development of a subdiaphragmatic abscess. The upper angle of the wound was separated to increase drainage. Postoperative diabetes was not discovered until the eighth day when the urine showed 4+ reduction. Fasting blood sugar was 273 mg. per 100 cc. Thereafter (see Fig. 2), insulin was administered with or without infusions as the case may have been. During the 26 days following operation fasting blood sugars varied from 132 to 400 mg. per 100 cc. depending upon the activity of the subdiaphragmatic abscess. During the 4 last days in the hospital fasting blood sugars varied from 100 to 126 mg. per 100 cc. She was discharged on the forty-second postoperative day with wound healed and no glycosuria.

During the winter of 1947–48, the patient was ambulatory and moderately active. By the end of March, 1948, there was recurrence of a palpable mass in the upper left quadrant of the abdomen and this gradually increased in size. There were periods of extreme thirst and a blood sugar determination showed 230 mg. per 100 cc., on one occasion, with reduction in the urine of +++ to ++++. Insulin in doses of 15 to 30 units a day was given. Recurrences of the neoplasm progressed until the patient died in June 1948, 8 months after the massive resection.

Case 2.—W. M., a 44-year-old salesman, was first seen at the Memorial Hospital on March 17, 1948, at which time the following history was obtained: In the early part of October, 1947, the patient first noticed occasional epigastric distress which had no relationship to the quality or amount of food ingested. This persisted and became associated with constipation and a feeling of general malaise. In November, 1947, the patient sought medical consultation for the first time and gastro-intestinal studies were suggestive of a gastric neoplasm. An exploratory laparotomy was advised but not accepted. The symptomatology gradually became more marked and in February, 1948, the patient finally submitted to laparotomy, performed in another institution, which revealed an extensive gastric carcinoma invading neighboring structures and, therefore, considered inoperable. The patient was made aware of the seriousness of his condition and he then sought further advice elsewhere.

Physical examination at the time of admission to the Memorial Hospital revealed a well-developed and well-preserved middle-aged male who was somewhat pale and showed evidence of some weight loss (20 pounds) but he was in no acute distress. In the abdomen there was a recently healed left upper paramedian scar and palpation revealed a large, firm, nodular mass somewhat fixed and poorly outlined in the epigastrium. The liver and spleen were not palpable. No other masses were palpated. There was no "rectal shelf" on digital examination.

Preoperative laboratory studies: (1) Blood chemistry: Blood sugar 81 mg. per 100 cc.; blood urea nitrogen 12.5 mg. per 100 cc.; serum protein 6.9 Gm. per 100 cc.; serum chlorides 100 mg. per 100 cc.; serum bilirubin 1.0; hematocrit 46 per cent; prothrombin 75 per cent. (2) Blood: Hemoglobin 85 per cent; white cells 7.8 (with a normal differential). (3) Urinalysis: specific gravity 1.008, reaction acid, albumen and sugar negative. (4) Chest film: negative for metastases.

Operation March 20, 1948. The findings were as follows: Large, firm tumor apparently arising in the upper portion of the stomach and invading by direct extension the transverse colon and body of pancreas. Fairly large, firm nodes were found along the lesser and greater curvatures. The liver was free of disease and there were no peritoneal implants. The surgical procedure consisted of total gastrectomy, splenectomy, partial pancreatectomy (tail and body), transverse colectomy en masse; esophago-jejunostomy;

enteroenterostomy; colocolostomy (end-to-end). The patient withstood the procedure well, receiving 3,500 cc. of blood and 1,000 cc. of normal saline during the operation.

Pathologic Report: "Adenocarcinoma, Grade III., of stomach invading pancreas, wall and mucosa of colon, metastatic to nodes on greater and lesser curvature. Negative spleen."

Postoperative Course: The immediate postoperative course was satisfactory. The blood pressure was maintained within normal limits and shock did not occur. The patient did not receive anything by mouth for 9 days and was given 3,000 cc. of parenteral fluids daily as follows: Mornings, 1,500 cc. 5 per cent glucose in saline; afternoons, 1,500 cc. 5 per cent glucose in distilled water. On the fourth postoperative day at 2:00 A.M. the patient's blood pressure fell from 120/90 to 80/60; there was profuse perspiration. The pulse was regular but somewhat weak and the remainder of the physical examination was negative. Blood transfusion was given. The urine was tested for sugar and was positive. A fasting blood sugar determination was then obtained and found to be 277 mg. per 100 cc.; 10 units of regular insulin were promptly administered. Thereafter the use of small amounts of regular insulin was enough to control the diabetic state, (see Fig. 3). Daily fasting blood sugar determinations were obtained thereafter. On the third postoperative day the patient was out of bed and on the ninth postoperative day he was allowed to receive fluids by mouth. He was discharged on the eighteenth postoperative day at which time there was no evidence of diabetes. Six months after operation the patient remains clinically well and is free from diabetes.

Case 3.—W. B., a 55-year-old white housewife who was first seen on April 15, 1948, at which time she gave the following history: In January, 1948, the patient first noticed some weakness and general malaise which was associated with slight epigastric distress together with some difficulty in swallowing. The patient saw her private physician who prescribed a diet and medication for symptomatic relief. She felt somewhat improved, but within a few weeks the symptoms recurred. A gastro-intestinal roentgenographic study was done and revealed the presence of a gastric neoplasm. The patient lost approximately 6 to 8 pounds in weight and had been on a soft diet for the 2 months prior to her appearance. Lately she had been complaining of a moderately severe pain in the back (pancreatic invasion?).

The past and familial histories were non-contributory. Physical examination at the time of admission showed a well-developed and well-nourished white female who was not in acute distress. There was some epigastric fullness and tenderness of the abdomen but no definite evidence of neoplasm was present; the liver was not enlarged and the spleen and kidneys were not palpable. Rectal and pelvic examination revealed no evidence of metastases.

Preoperative laboratory studies: (1) Blood chemistry: serum chlorides 106 mg. per 100 cc.; serum protein 6.0 Gm. per 100 cc.; blood sugar 71 mg. per 100 cc; blood urea nitrogen 12.0 mg. per 100 cc. (2) Blood: hemoglobin 95 per cent; white cells 6.4. (3) Urinalysis: specific gravity 1.026; reaction acid; amber color and negative for sugar and albumen. (4) Chest film: negative for metastases.

Operation April 27, 1948. A large fungating lesion was found apparently arising very high in the lesser curvature of the stomach; the tumor had invaded almost the entire stomach and was firmly adherent and fixed to the body of the pancreas; the liver was free from disease and there were no peritoneal implants. The surgical procedure consisted of resection of the entire stomach and omentum; splenectomy; and partial pancreatectomy (tail and body). The operation was completed by esophagojejunostomy and enteroenterostomy. The patient withstood the procedure well and received 1,500 cc. of blood and 500 cc. of saline during the operation.

Pathologic report: "Adenocarcinoma Grade IV of stomach; proximal and distal lines of resection are clear of tumor; diffuse lymphatic permeation of gastric wall by tumor with invasion of pancreas and metastases to omental nodes; negative spleen."

Postoperative course: The immediate postoperative course was uneventful. The blood pressure was satisfactorily maintained within normal limits following the operation and shock did not occur. The patient received 3000 cc. of parenteral fluids daily as follows: 1000 cc. of amigen in the mornings and 2000 cc. of 5 per cent glucose in distilled water (or saline) in the afternoons. On the first postoperative day fasting blood sugar determination revealed the presence of a hyperglycemia and thereafter an increasingly severe diabetic state persisted until death on the twelfth day (See Fig. 4). The patient sat up on the second postoperative day and was out of bed on the fourth day. On the sixth postoperative day there was acetone in the urine for the first time. On the eighth postoperative day the patient had a sudden, sharp pain in the right lower chest which was associated with anxiety and shortness of breath; chest examination was entirely negative and the legs showed no evidence of phlebo-thrombosis. A tentative diagnosis of small pulmonary infarct was made. On the following day chest examination revealed a definite dullness in the right lower lobe posteriorly; a chest film was reported as not indicative of pulmonary infarct. On the tenth postoperative day there was a definite swelling of

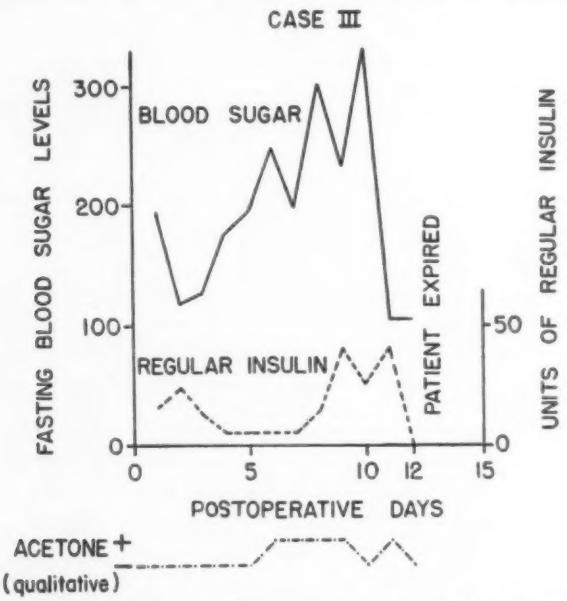


FIG. 4.—(Case 3.) Graph of morning fasting blood sugars showing postoperative diabetic state. Patient died on the twelfth day.

the left leg. On the twelfth postoperative day the patient's condition deteriorated rather rapidly and she expired. Necropsy was not obtained. The rather sharp increase in the diabetic state after the fifth postoperative day is indicative of some disturbance probably associated with the fatal outcome but the exact nature of which was not determined in the absence of necropsy.

DISCUSSION

Post partial pancreatectomy diabetes in man where the pancreas was presumably normal does not appear to have been previously cited in the literature. However, in the case where the pancreas presented inflammatory disease it has been noted. Mallet-Guy, Chambon and Plauchu[3] describe a patient in whom there was mild preoperative diabetes (glycemia, 160 mg. per 100 cc.) and

following resection of 40 Gm. of the body and tail, which portions were enlarged and tumefied (histologic study showed chronic fibrous pancreatitis), the fasting blood sugar reached levels of 176, 208 and 301 mg. per 100 cc. on three days respectively. Insulin was administered in daily doses up to 60 units and by the end of 15 days fasting blood sugars were again at normal levels. Mallet-Guy interprets these findings as indicating that the presence of a large inflammatory process in the pancreas interferes with its normal function, hence the preoperative diabetes, and that resection of the affected areas permitted a return to normal function of the remaining unaffected portions of the gland, hence the eventual disappearance of the diabetes.

In the case cited by Leriche[4] the patient was diabetic before subtotal pancreatectomy was performed for severe pain due to marked chronic pancreatitis with pancreato-lithiasis. In the weeks following the operation the diabetes seemed to increase in severity. This is explained by the disease, already present in the remaining portion of pancreas, which might have continued to progress.

In the three patients herein reported the pancreas was presumably normal in each instance. Following resection of the body and tail, the remaining head of the organ appeared unprepared to function normally for carbohydrate metabolism. This led to the use of insulin. In Case 1, the diabetic state lasted for practically three weeks after its discovery on the eighth postoperative day. In Case 2, no insulin was required after the thirteenth day. The third patient succumbed before opportunity was afforded to observe the duration of the surgically induced diabetes but the latter was severe due to disturbances of unknown type and, as stated, undoubtedly associated with the fatality.

The recurrence of diabetes in Case 1, a few months after its apparent subsidence, suggests further destruction of the remaining pancreas by recurrent neoplasm. Another explanation is that the patient might have been in the process of developing diabetes and that the resection of most of the pancreas hastened the evolution of this condition. It is interesting to speculate upon the question of whether or not these patients who did develop the transitory postoperative diabetes were in the process of developing the disease but had not yet manifested it clinically. This appears to be a logical hypothesis to explain why a few patients do and most patients do not develop transitory diabetes following resection of the body and tail of the pancreas.

SUMMARY

Case histories are presented showing the development of diabetes following resection of the body and tail of the pancreas for secondary invasion by gastric cancer. The pancreatic tissue itself in these patients appeared normal on histologic examination.

Postoperative diabetes is to be anticipated in some instances where the body and tail of a presumably normal pancreas are excised. The immediate prognosis of such a diabetic state appears to be good since the induced diabetes seems to be transient.

BIBLIOGRAPHY

1 Brunschwig, A.: The Surgery of Pancreatic Tumors. C. V. Mosby and Co., St. Louis, Mo., 1942.

Brunschwig, A.: One Stage Pancreatoduodenectomy. Surgery, Gynec. and Obst., **85**: 161, 1947.

2 Brunschwig, A., A. T. Ricketts and R. R. Bigelow: Total Pancreatectomy, Total Gastrectomy, etc. in a Diabetic Patient. Surg., Gynec. and Obst., **80**: 252, 1945.

3 Mallet-Guy, P., J. Chambon and M. Plauchu: Return to Normal of Hyperglycemia Due to Chronic Pancreatitis as a Result of Left Hemipancreatectomy. Lyon Medical, May, 1936, No. 22.

4 Leriche, R.: Subtotal Pancreatectomy for Pain Due to Pancreatolithiasis with Hyperglycemia. Mem. Acad. de Chirurgie de Paris, Jan. 1948, Vol. 74, p. 57.

THE CLINICAL USE OF POLYETHYLENE TUBING FOR INTRAVENOUS THERAPY*

A REPORT ON SEVENTY-TWO CASES

B. J. DUFFY, JR., M.D.

NEW YORK, N. Y.

FROM THE DEPARTMENT OF CLINICAL INVESTIGATION, THE SLOAN-KETTERING INSTITUTE, MEMORIAL CANCER CENTER, NEW YORK, N. Y.

INTRODUCTION

INTRAVENOUS THERAPY may present serious difficulties in the management of the severely ill patient. The number of veins available for parenteral treatment often diminishes alarmingly through sclerosis, from trauma and overuse. Patient welfare and the efficiency of the house staff are severely affected.

Indwelling needles have been tried in the past, but they have obvious deficiencies.[1] The sharp point and inflexibility unduly traumatize the vein and make it difficult to maintain the needle in the vein without seriously limiting the patient's movements. Clotting of the needle and phlebitis of the injected vein are common complications. The need for a practicable method of venous intubation has increased with frequent use of large infusions in surgical and medical practice. At the suggestion of Dr. H. W. Smith of New York University, the use of plastic tubing for intravenous infusions was investigated.

The purpose of this paper is to demonstrate that these difficulties may be overcome by intravenous catheterization with plastic tubing. The tubing used was polyethylene (polythene)† in postoperative patients on the surgical service at Memorial Hospital.‡ There have been scattered references to intravenous plastic tubing in the literature,[2-5] but thus far these have represented small series of patients in whom the cannula was in place for a relatively short period of time.

Zimmerman[2] discussed the use of a vinylite tube in 11 dogs for periods of from four to five weeks without untoward effects. Venous thromboses were found in two dogs and were thought to be due either to the sclerosing properties of the injected solutions or to the mere presence of the plastic

* This study was aided by grants from the National Institute of Health, National Cancer Institute, Bethesda, Maryland; The American Cancer Society, Incorporated, New York; and the Damon Runyon Cancer Fund, New York. Submitted for publication March, 1949.

† The tubing and equipment were obtained from Becton Dickinson Company, Rutherford, N. J., through the courtesy of Mr. Oscar Schwidetsky.

‡ The cooperation of the surgical staff of Memorial Hospital is gratefully acknowledged.

catheter in the vein. MacQuigg[6] reported a series of observations using a polyvinyl chloride tubing for intramuscular injections in humans.

Meyers[3] was the first to report the clinical use of polyethylene* tubing. He used polyethylene tubing in administering heparin and plasma to two patients for a period of several days. Guenther, *et al.*,[4] used polyethylene tubing for intravenous therapy in 18 cases for periods up to two weeks. They noted "the most satisfactory results were obtained in continuous infusion of solutions of penicillin and heparin." Diamond and Thomas[5] have used polyethylene tubing of large caliber in the treatment of newborn babies with erythroblastosis. The tubing was inserted through the umbilical vein into the vena cava and left in place for three hours. Five hundred cubic centimeters of the infant's blood was replaced with Rh negative blood, and no reaction of the veins was noted.

There have been two extensive experimental studies[7, 8] with polyethylene in neuro-surgery in which the plastic was shown to fulfill the requirements of a dural substitute. Segments of polyethylene tubing implanted into the brain for as long as 90 days caused no significant inflammation. In contrast, another plastic, cellophane, when implanted into brain tissue caused an early and marked inflammation with leucocytosis and gliosis.

Poppe and De Oliveira[9] investigated methods of obliterating aneurysms by inducing fibrosis around them with irritating plastic films. They used a material "polythene cellophane" in four human cases and produced marked fibrous reactions around the aorta. This was attributed to the use of an impure plastic. Yaeger and Cowley[10] have recently used polyethylene as a fibrous tissue stimulant in the treatment of aneurysms and recurrent hernias. Pure polyethylene had no tissue reaction whereas polyethylene with dicetyl phosphate retained from its preparation produced a marked reaction.

Hurwitt[11] recently reported the use of polyethylene tubing in animals as a vascular shunt to overcome pulmonary stenosis. Hackworth[12] replaced the thoracic aorta with polyethylene in dogs. In both studies clotting in the tube, and tissue reaction, were reported minimal.

Ferris and Grindlay[13] have adapted polyethylene to various urologic procedures. Both polyvinyl chloride and polyethylene had distinctly less encrusting from urinary salts and organic material than the usual rubber catheter.

Brown[14] and his co-workers have attempted direct methods of anastomosing the common bile duct, trachea, and pelvic colon respectively with molded polyethylene tubes. In these studies they noted no tissue reaction to polyethylene and no tendency for the plastic to deteriorate or for the tubes to become blocked with secretions or solid material.

DESCRIPTION OF POLYETHYLENE

Industry has developed a large variety of plastics but very few have been found to be sufficiently well tolerated in tissue to be of value in surgical

* "Med-o-seal," A. C. Balfour Co., Englewood, N. J.

work. Studies with polyethylene have produced such varying results that it is of vital necessity that those using it be absolutely familiar with the physical and clinical properties of the product.

Polyethylene (polythene, Med-o-seal) is a thermo-plastic, synthetic resin and has probably the simplest formula of all the plastics. It consists of carbon atoms joined into chains, each carbon carrying two atoms of hydrogen. These chains consist of several hundred to more than a thousand such units with a molecular weight of approximately 18,000.

Polyethylene is produced commonly by two methods. The first is by "solvent cast" with the use of stippling agents, plasticizers and antioxidants. This frequently results in an impure plastic as noted by Yaeger and Cowley.[10] The preferable method of preparation is by "extrusion," wherein the plastic is converted by heat and pressure into the desired tubing.

The latter product, which we found best adapted to our uses, is flexible, chemically inert, fluid repellant, and inexpensive. It is not affected by concentrated hydrochloric, sulfuric, and hydrofluoric acids, and it resists concentrated sodium hydroxide. The plastic is resistant to tissue fluids at body temperature for prolonged periods. It has the non-coagulant property that characterizes paraffinic products when they are brought into contact with blood.

METHOD OF STUDY

A. *Choice of patients.* The patients in this series ranged in age from 18 months to 74 years. They were, in general, studied following major surgery, when intravenous therapy was extremely difficult and in a few instances almost impossible. The technic was employed solely by the Department of Clinical Investigation at the request of the surgical services. A close record was kept indicating length of time that the tubing was left inserted, type of solution given through the tube and any complications which ensued.

B. *Technic.* Two different calibers of tubing were available. The smaller caliber (for penicillin and heparin therapy) passed through a thin wall BD No. 17 needle. The larger, which was used when blood, plasma, or protein solutions were to be administered, or when rapid infusion might be needed, was inserted via a No. 14 BD needle. The intravenous tubing and accessories set are kept as a unit on a small cart which can be readily transported to the bedside (Fig. 1). It has been our practice to boil the tubing in glass tubes which prevent bending of the plastic. They are then stored in a tray containing 1 to 1000 aqueous solution of benzalkonium chloride (Zephiran Chloride NNR). Polyethylene does not withstand autoclaving, due to its low melting point.

The appropriate vein is selected and the field prepared and draped with the usual sterile precautions. A small amount of 1 per cent novocaine is given intradermally and subcutaneously, and a small incision is made with a No. 5 Bard Parker blade.

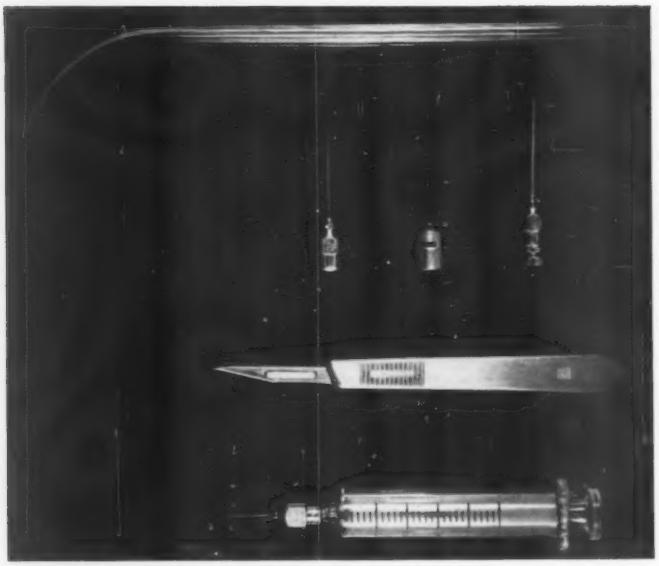


FIG. 1.—Unit of intravenous tubing and accessories.

FIG. 2

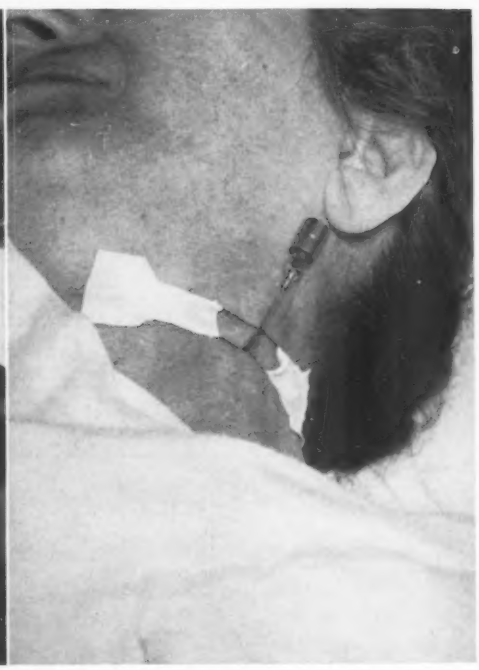


FIG. 3

FIG. 2.—Insertion of tubing after the syringe is detached, and with the needle held carefully in place, the plastic tubing is passed into the vein.

FIG. 3.—Jugular tubing maintained in place with a butterfly adhesive and suture tied around it.

The thin wall No. 14 BD needle is inserted into the vein using a 5 cc. syringe loaded with 1 cc. of heparin, a small amount of which is injected into the needle as soon as it enters the vein. The syringe is then detached and, with the needle held carefully in place, the plastic tubing is passed into the vein for a varying length, depending on the site selected. (Fig. 2) A small amount of heparin is instilled into the plastic tube prior to insertion. With digital pressure over the vein, holding the tubing in place, the needle is withdrawn. A blunt nosed No. 18 BD needle is inserted into the free end of the tubing and the remaining heparin injected into the tube to prevent clotting.

If an infusion is to be started it may be attached by using a Luer-Lok adaptor. Otherwise the tube may be effectively sealed off with a Luer-Lok plug. Jugular tubing is best maintained in place with a butterfly adhesive and suture tied around it. (Fig. 3) Elastic adhesive adds stability and is sufficient when the femoral vein is used.

The tubing is rinsed out with sterile isotonic saline following plasma or blood infusions. Following each use, or at least twice a day, ½ to 1 cc. of heparin* should be instilled into the tube. This may be discontinued after the first four to five days if the tube is being maintained with constant infusions of isotonic aqueous solutions.

Changes of the direction and position of the tube are sometimes necessary to permit freer movement of the patient and more ease in infusing and withdrawing specimens through the tube. The withdrawal of blood specimens is facilitated by the use of a tube with several lateral openings at its distal end. Continuous intramuscular therapy may be carried out by the insertion of the smaller catheter through a long No. 17 BD thin wall needle under the fascia lata of the thigh.

C. *Choice of vein.* The arm, while frequently presenting large veins, has obvious limitations. The catheter must be inserted proximal to the ante cubital fossa to avoid valves and bending at the elbow. Arm motion also causes mechanical irritation of the vein by the tubing unless it is inserted for a sufficient distance to enter a large vessel. It has been our experience that when the tubing occludes the vein, edema results, probably as a result of mechanical irritation. In this study the large veins, *i.e.,* jugular and femoral, were found to be the most satisfactory location for intravenous catheterization.

RESULTS

The tubing first utilized in this study was polyvinyl chloride similar to the one used by McQuigg for intramuscular injections. In our preliminary series of eight patients several local reactions† occurred which led to the use of polyethylene on the theory that it represented a purer plastic.[15]

* Five to 10 mg. Heparin Sodium, Upjohn.

† We believe these reactions were due to impurities in the preparation of this tubing since we are now using a BD polyvinyl tubing with excellent results.

The observations made in this study are summarized in Figures 4 and 5. Successful intubation was achieved in 54 cases out of a total of 72. The results were completely satisfactory in 42 cases out of 48 where large veins (jugular and femoral) were catheterized. In no cases was it impossible to introduce the

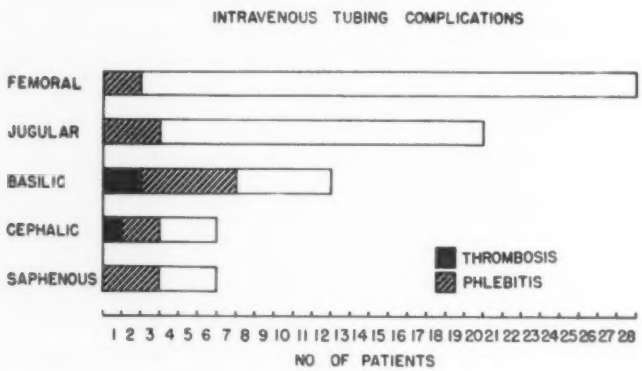


FIG. 4

tube, although repeated attempts were necessary in some instances. One jugular tube remained patent for 39 days and was removed electively without complication.* A femoral tube was similarly effective for 35 days.

Symptoms of mild phlebitis were noted in 16 cases. These consisted of a temperature elevation, and pain, or edema in the area intubated. Frank throm-

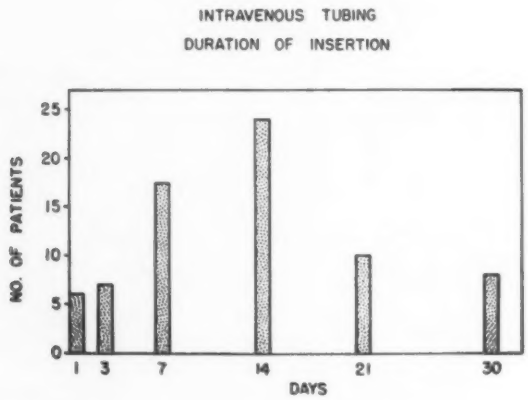


FIG. 5

bosis was encountered in three cases where smaller veins were used. It is interesting that these thromboses occurred at three, eight and 17 days respectively. We have tended to be conservative and remove the tubing at any evidence of local reaction.

* A short clinical history of the patient is appended to this report.

DISCUSSION

Intravenous catheterization has proved its value in this series of 72 patients. The indwelling tubes alleviated patient discomfort and were convenient and time saving to the house staff. The tubing was well tolerated and provided considerable patient mobility. Blood, plasma, and hypertonic solutions were given without difficulty and at a satisfactory rate.

From the data reported above, it appears that the biggest disadvantage of indwelling intravenous catheters is local irritation to the vein. This irritation is probably mechanical in nature since it tended to occur where small veins were used. This drawback was circumvented by intubating the jugular (cervical) or femoral veins. Close observation during the initial period to insure proper placement and function of the tube is desirable. Thus, the possible complication of too rapid infusion is obviated. The theoretical possibility of aspiration of air is prevented by having the patient in a recumbent position with the open end of the tubing below the heart when specimens are withdrawn or infusion started. Careful technic with the femoral puncture is indicated to prevent possible reflex arterial spasm. In patients who have undergone extensive lower abdominal surgery we do not use the femoral route due to the possibility of further complicating an established phlebitis.

Further modifications of technic, particularly the use of a smaller tubing for peripheral veins, are indicated. Such a plastic tubing inserted in the operating room under anesthesia at the beginning of the operation would add to the patient's comfort and facilitate parenteral therapy during the early postoperative period.

SUMMARY

Therapy was carried out by means of indwelling intravenous polyethylene tubing in a series of 72 cases.

Ten local reactions, including three frank thromboses, were encountered in 18 patients whose arm veins were used. Six minor reactions occurred in 43 patients in whom the jugular or femoral veins were employed.

In one case the tubing was maintained for 39 days.

The procedure of intubation is presented and its limitations and advantages are discussed.

CASE HISTORY

M. P., Hospital No. 75596, a 26-year-old female with Hodgkins disease was admitted to the Research Ward for study of a progressive anemia following radiation and HN_2 therapy.

It was felt that the possibility of hypersplenism suggested by the anemia and the splenomegaly justified splenectomy, which was carried out on January 17, 1948. The operation was complicated by a severe hemorrhage, necessitating intra-arterial transfusion.

Venipuncture was extremely difficult in the immediate postoperative period due to shock, multiple vein ligations and sclerosis from previous chemotherapy. A polyethylene tube was inserted into her left jugular vein on the first postoperative day.

For several weeks parenteral feeding and hydration were carried out through this tube. As much as 3500 cc. of fluids were administered in 24 hours without any difficulty or discomfort. Infusions were stopped nightly without plugging of the tube.

After 39 days the tube was removed, and the patient was discharged. The jugular vein was not palpably thickened. The small sinus tract which remained, healed completely in 24 hours.

BIBLIOGRAPHY

1 Riddell, W.: Blood Transfusions, p. 155, 1942, London, Oxford.

2 Zimmerman, B.: Intravenous Tubing for Parenteral Therapy. Science, **101**: 567, 1945.

3 Meyers, L.: Intravenous Catheterization. Am. J. Nursing, **45**: 930, 1945.

4 Guenther, T., J. Grindley and J. Lundy: New Flexible Capillary Tubing for Use in Venoclysis. Proc. Staff Meet. of the Mayo Clinic, **22**: 206, 1947.

5 Diamond, L. K., and W. O. Thomas: Replacement Transfusions in the Treatment of Severe Erythroblastosis Fetalis by a Single Plastic Catheter in the Umbilical Vein. (In Press)

6 MacQuigg, R.: New Technique for Parenteral Fluid and Drug Administration. Surgery, **18**: 592, 1945.

7 Brown, M. H., J. H. Grindley and W. McK. Craig: The Use of Polythene Film as a Dural Substitute. Surg., Gynec. & Obst., **86**: 663, 1948.

8 Ingraham, F. D., E. Alexander, Jr., and D. D. Matson: Polyethylene, A New Synthetic Plastic for Use in Surgery—Experimental Application in Neuro-Surgery. J. A. M. A., **135**: 82, 1947.

9 Poppe, J. K., and Renault H. de Oliveira: Treatment of Syphilitic Aneurysms by Cellophane Wrapping. J. Thoracic Surg., **15**: 186, 1946.

10 Yaeger, G. H., and R. A. Cowley: Studies on the Use of Polythene as a Fibrous Tissue Stimulant. Ann. Surg., **128**: 509, 1948.

11 Hurwitt, E. S.: Experimental Approach to Increasing Blood Supply of Lungs. Surg., Gynec. & Obst., **87**: 313, 1948.

12 Hackworth, L.: Replacement of the Thoracic Aorta with Polyethylene Tubing. Reported at American College of Surgeons, N. Y., N. Y. September 11, 1947.

13 Ferris, D. O., and J. H. Grindlay: Use of Polythene and Polyvinyl Tubing in Ureterostomy, Nephrostomy and Cystostomy. Proc. Staff Meet. of the Mayo Clinic, **23**: 385, 1948.

14 Brown, M. H., J. H. Grindlay and W. McK. Craig: Preliminary Report on Experimental and Clinical Studies with Polythene Film. Proc. Staff Meet. Mayo Clinic, **22**: 453, 1947.

15 Ingraham, F. D., E. Alexander, Jr., and D. D. Matson: Plastics in Surgery, New England J. Med., **236**: 402, 1947.

THE EFFECT OF DIATHERMY UPON ABDOMINAL ADHESIONS*

AN EXPERIMENTAL STUDY

RAYMOND K. MINGE, M.D. AND CLARENCE DENNIS, M.D.

MINNEAPOLIS, MINN.

FROM THE DEPARTMENTS OF SURGERY OF UNIVERSITY OF MINNESOTA AND OF THE MINNEAPOLIS GENERAL HOSPITAL

USE OF DIATHERMY IN PROPHYLAXIS OF ABDOMINAL ADHESIONS

Historical background. Smith[1] in 1940 reported the use of fever therapy in two cases of mechanical small bowel obstruction due to pelvic inflammatory disease. These cases had both been characterized by repeated episodes of bowel obstruction due to intraperitoneal adhesions resulting from old gonococcal pelvic infection. Following fever therapy treatments using the Kettering hypertherm for two to three hours at intervals of one to three days for four to six treatments further episodes of intestinal obstruction did not occur. The value of hyperthermia in cases of gonococcal and non-specific pelvic inflammatory disease had been previously noted by other workers in this field.

During the period of 1942-3 ten cases of bowel obstruction due to intraperitoneal adhesions were treated at the University of Minnesota Hospitals with short wave diathermy following enterolysis. The following case is cited as an example:

Case History.—In 1919 this 42-year-old male (U. H. No. 725832) had an appendectomy for a perforated appendix. Subsequent to this operation two laparotomies had been performed for adhesive bowel obstruction. In 1942 a total colectomy was performed at the University of Minnesota Hospitals; numerous adhesive bands were divided at the time of this operation. Two weeks later the patient developed a mechanical small bowel obstruction due to adhesive bands. Laparotomy and enterolysis were performed. During the first seven postoperative days the patient received short wave diathermy treatments. Three 15-minute treatments were given daily, employing the coil with 135–140 M. A. dosages. The subsequent course was uneventful and no further attacks of bowel obstruction ensued.

No specific therapeutic effect of short wave has ever been shown other than that due to the heat production within the tissues. Carlson and Orr[2] studied the effect of heat applied to the abdomen of dogs. Moist flannel covered by an electric pad at a temperature of 106-109° F. was used for one hour and the temperature in the midcolon checked by means of a long rectal thermometer. An average rise of temperature within the colon of 1.2° F. and an average body temperature rise of .5° F. was noted. Kymographic tracings of the dog's jejunum made during the application of heat showed no change in intestinal tone or movements. They also found that the prolonged (three hours) application of heat did not cause any significant increase in the intra-abdominal temperature. Tuttle and Fitts[3] studied the effect of short

* Supported by a Research Fund from the Graduate School of the University of Minnesota. Submitted for publication March, 1949.

wave diathermy on various phases of skeletal muscle activity and found all phases to be shortened with the greatest change occurring in the period of relaxation. Schlaepfer[4] noted a slightly increased rate of intestinal contraction after diathermy, but no increased strength of the contractions. He found little roentgen-ray evidence of increased intestinal activity with diathermy.

On the basis that short wave diathermy appeared to have had a favorable effect on redevelopment of intraperitoneal adhesive bowel obstruction in the patients so treated at the University of Minnesota Hospitals, an experimental study was carried out on dogs to determine the effect of diathermy on intra-abdominal adhesions.

Methods of producing adhesions. Two technics were employed to produce the adhesions:

1. In one series of dogs adhesions were produced by rubbing the terminal two feet of small bowel with dry gauze followed by the application of 7 per cent tincture of iodine to the traumatized bowel. Laparotomy was repeated two to four weeks later and the extent of adhesive formation was estimated. The usual finding was a coiling up of the terminal two feet of small bowel with dense adhesions between the coiled loops and adhesive bands between the traumatized bowel and parietal peritoneum and omentum. The adhesions were divided by sharp dissection with careful attention to hemostasis.

2. Ordinary glove talcum powder was used to produce adhesions. Under intravenous nembutal anesthesia the terminal two feet of small bowel was very gently scarified with dry gauze and a minute amount of autoclaved talc powder (always less than .5 Gm.) was dusted over this bowel surface and the abdomen closed. Laparotomy was repeated one to three weeks later and in every instance dense adhesive formation had resulted. The traumatized bowel was usually coiled up in a dense adherent mass with the omentum adherent thereto. Small granulomatous areas were usually present on the mesentery, omentum, and serosal surface of the small bowel.

General effects of diathermy. Observations were made on the effects of short wave diathermy on the exposed bowel, intra-abdominal and rectal temperatures and respiratory rate of the anesthetized dog and on the rectal temperature and respiratory rate of the non-anesthetized dog. Increased respiratory rate is the outstanding effect of short wave diathermy on the dog. Respirations become rapid and panting within a few minutes after the application of the diathermy coil or pads.

The average respiratory rate of a dog at rest is 15 to 25 a minute. Diathermy rapidly increased the rate to 100 to 300 per minute. Hemingway[5] has shown that this increased rate is associated with a decreased tidal volume, supporting the theory that the heat stimulation causes a rapid air movement over the moist surfaces of the mouth, tongue, and pharynx without too great an air movement in the lung alveoli.

Effects of diathermy on the anesthetized dog. The dogs were anesthetized with intravenous nembutal, the diathermy pads applied to the sides of the abdomen, the abdomen opened through a midline incision, and observations

made on the local effects on the exposed bowel, intra-abdominal and rectal temperatures, and respiratory rate. Within a few minutes after institution of the diathermy treatment, the bowel became edematous and hyperemic and small droplets of fluid appeared on the serosal surface. Increased peristaltic activity, manifested by increased rate and strength of intestinal contractions, was noted.

TABLE I.—*Effects of Diathermy on Anesthetized Dog*

Dog No.	Dosage (M.A.)	Length of Treatment	Total Temperature Rise		Respiratory Rate Per Minute		Rectal Temperature Rise During First 15 Min. of Diathermy	Respiratory Rate Increase During First 15 Min. of Diathermy
			Rectal	Intra-abd.	Initial	Final		
1. No. 9	3,000	70 min.	3.3°C	3.7°C	20	260	1.7°C	24
2. No. 5	4,500	27 min.	7. °	8. °	20	300	1.5°	16
3. No. 6	3,000	145 min.	4.4°	....	16	208	1.4°	70
4. No. 29	3,000	45 min.	3.9°	4.6°	12	86	1.4°	2

Table I summarizes the effects of diathermy on the anesthetized dog. Dogs No. 4, 5, 6 and 29 expired after a precipitous rise in temperature. Autopsy revealed a grayish cooked appearance to the small and large bowel, with congestion, edema, and petechial hemorrhages scattered over the serosa and mesentery. The abdomen was not reopened in dog No. 6.

Table II summarizes the effects of diathermy on the non-anesthetized dog. With identical dosages of diathermy the maximum rectal temperature

TABLE II.—*Effects of Diathermy on Non-Anesthetized Dog*

Dog No.	Dosage (M.A.)	Length of Treatment	Total Temperature Rise (Rectal)	Respiratory Rate Increase		Rectal Temperature Rise During First 15 Min. of Diathermy	Respiratory Rate Increase During First 15 Min. of Diathermy
				Initial	Final		
1. No. 8	3,000	30 min.	.6°C	26	180	.4°C	155
2. No. 9	3,100	110 min.	.2°	80	320	0	180
3. No. 10	3,000	65 min.	1.6°	40	280	1.6°	170
4. No. 11	4,500	40 min.	.3°	100	260	.3°	140

rise was 7° C. in the anesthetized dog as compared to 1.6° in the non-anesthetized dog. There was a lag in the increased rate of respiration in the anesthetized dog receiving diathermy, two of the four dogs showing little change until shortly before death. The best guide as to diathermy effect in the non-anesthetized dog was the respiratory rate. There was no safe guide as to what constituted a safe dosage of diathermy in the anesthetized dog.

EXPERIMENTAL STUDY ON USE OF SHORT WAVE DIATHERMY IN RELATIONSHIP TO FORMATION OF INTRA-ABDOMINAL ADHESIONS

In the experimental study to be described the diathermy treatments were not begun until the first postoperative day. The treatments were given for prolonged periods (one to six hours) and the dosage guided by the tolerance

of the dog. When the dog showed evidence of fatigue and excessive panting respiration the heat was discontinued for a few minutes. In one dog diathermy treatment was instituted immediately after completion of enterolysis and while the dog was still under the influence of the anesthetic. After one hour the temperature showed a precipitous rise, respirations became shallow and irreg-

TABLE III.—*Diathermy Treated Dogs*

Dog No.	Method of Producing Adhesions	Average Dosage	Duration of RX Daily (Average)	Temp. Rise (C) (Average)	Resp. Rate Rise (Average)	No. of Days Dia-thermy RX Given	Degree of Reformation of Adhesions After Diathermy RX	Bowel Obst.
1. No. 49	Tr. iodine	3800 M.A.	60 min.	.6°	20–200	10	More extensive	No
2. No. 52	Tr. iodine	3600 M.A.	80 min.	.4	16–210	14	Slightly less	No
3. No. 53	Tr. iodine	3500 M.A.	75 min.	.5	20–230	9	More extensive	No
4. No. 38	Tr. iodine	4000 M.A.	60 min.	1.1	18–190	7	More extensive	No
5. No. 13	Talcum powder	3500 M.A.	180 min.	.4	28–240	4	More extensive	No
6. No. 16	Talcum powder	3200 M.A.	250 min.	.5	34–260	6	More extensive	No
7. No. 17	Talcum powder	3400 M.A.	200 min.	.3	48–215	7	More extensive	No
8. No. 25	Talcum powder	3600 M.A.	180 min.	.2	20–200	9	More extensive	No
9. No. 18	Talcum powder	3500 M.A.	160 min.	.3	26–216	8	More extensive	No
10. No. 27	Talcum powder	3500 M.A.	180 min.	.3	24–200	9	More extensive	No
11. No. 10	Talcum powder	Dog expired while receiving diathermy immediately p.o. and while yet under anesthesia						

ular, and death quickly ensued. The reason for the intolerance to diathermy under general anesthesia is not clear, but the danger was sufficiently definite to contraindicate its continued use in the anesthetized animal.

Two series of experiments were run, one employing tincture of iodine and the other talcum powder to produce the adhesions. A total of 22 dogs was

TABLE IV.—*Controls*

Dog No.	Method of Producing Adhesions	Degree of Reformation of Divided Adhesions	Bowel Obstruction
1. No. 47	Tr. of iodine	Greater	No
2. No. 54	Tr. of iodine	Greater	No
3. No. 55	Tr. of iodine	Greater	No
4. No. 44	Tr. of iodine	Greater	No
5. No. 56	Tr. of iodine	Greater	No
6. No. 2	Talcum powder	Greater	No
7. No. 14	Talcum powder	Greater	No
8. No. 19	Talcum powder	Same	No
9. No. 1	Talcum powder	Greater	Yes
10. No. 8	Talcum powder	Greater	Yes
11. No. 12	Talcum powder	Greater	Yes

studied, 11 of which served as a control group. Laparotomy was performed three to four weeks after the production of the adhesions and a quantitative estimate made of the extent of the adhesive process. Diathermy treatments were begun the following day and given daily thereafter for four to 14 days. Laparotomy was repeated one to two weeks following the last diathermy treatment and again a quantitative estimate made of the extent of adhesive

formation. Tables III and IV summarize the data in the diathermy treated and the control series of dogs.

Summary. The clinical impression that short wave diathermy is of value in prevention of formation of intra-abdominal adhesions was not substantiated by experimental evidence. Although no obstruction occurred in the treated group of dogs, the extent of reformation of divided peritoneal adhesions was the same in the diathermy-treated dogs as in the control series.

BIBLIOGRAPHY

1 Smith, B. A. Jr.: Fever Therapy in Treatment of Mechanical Intestinal Obstruction Due to Pelvic Inflammatory Disease. Surgery, **7**: 61, 1940.

2 Carlson, H. E., and T. G. Orr: Penetration of Moist Heat Applied to Abdomen and Its Effect on Intestinal Movements. Arch. Surg., **30**: 1036, 1935.

3 Tuttle, W. W., and L. Fitts: Effect of Heat Produced by Shortwave Diathermy on Activity of Muscle. Lab. & Clin. Med., **29**: 609, 1944.

4 Schlaepfer, K.: Short Wave in Surgery. West. J. Surg., **29**: 153, 1941.

5 Hemingway, A.: Panting Response of Normal Unanesthetized Dogs to Measured Dosages of Diathermy Heat. Am. J. Physiol., **122**: 511, 1938.

THE EFFECT OF DICUMAROL UPON POSTOPERATIVE PERITONEAL ADHESIONS*

BEVERLY H. WHITE, M.D.†

BALTIMORE, MARYLAND

FROM THE SURGICAL HUNTERIAN LABORATORY, JOHNS HOPKINS MEDICAL SCHOOL, BALTIMORE.

Reports by Lehman and Boys[1-5] and Miki and Santani[6] have suggested that the incidence and extent of postoperative peritoneal adhesions may be reduced by the introduction of heparin into the peritoneal cavity at the time of operation and in the early postoperative period. Subsequent work[7] seems to cast doubt on the effectiveness of this means of therapy. Since this problem is in a state of flux and since no adequate means of therapy is available at the present, this study was undertaken to determine the effect of Dicumarol‡ on peritoneal adhesions. Dicumarol, like heparin, is a potent anticoagulant, although its mode of action is different.[8-11] However, the end result in regard to fibrin formation is the same.[12-14] The method by which healing and hence adhesion formation occurs is well known and will not be reviewed here. Suffice it to say that fibrin must be present before the formation of scar tissue can take place. The rationale behind the use of anticoagulants to diminish the development of peritoneal adhesions depends upon their ability to effect a reduction in the amount of fibrin which can be formed.

Adequate animal experimentation and clinical use have already shown that surgical procedures can be safely carried out in the presence of a lowered prothrombin activity produced by Dicumarol, provided complete hemostasis is obtained before the incision is closed.[8]

METHODS

Twenty-six healthy mongrel dogs, weighing from 4.8 to 11.5 Kg. were used in these experiments. They were divided into three groups: (1) a control group of six animals, (2) an experimental group of 14 animals, and (3) a severely dicumarolized group of six animals.

In groups one and two, preliminary operation consisted of laparotomy and abrasion of the serosal surface of the small bowel with dry gauze. Four segments of bowel 15 cm. long and equally spaced between the ligament of Trietz and the ileocecal valve were rubbed lightly with a pad of dry surgical gauze. Slight oozing of the rubbed area was produced intentionally in all cases. This bleeding ceased spontaneously before closure. The surface area of the serosa damaged by this procedure was approximately 150 square cm. At the close of the operation 2.5 Gm. of crystalline sulfanilamide was sprinkled in the peritoneal cavity to aid and abet the formation of adhesions.[15]

All animals were anesthetized with intravenous Nembutal (initial dose 30 mg. per Kg.; additional amounts as necessary). Hemostasis in all opera-

* Submitted for publication January, 1949.

† William Stewart Halsted Fellow in Surgery.

‡ Dicumarol is the registered collective trademark of the Wisconsin Alumni Research Foundation, which controls the use thereof.

tions was obtained by fine silk ligature, warm saline packs and by use of the electrocautery. No dressings were used on the operative incisions.

Originally it was planned to count the number of adhesions which formed following this procedure, but this method was found to be undesirable in that a true picture of the actual amount of serosa involved could not be obtained. Consequently, it was decided to estimate the area left bare of serosa after division of the adhesions (bare area).

Eleven to 35 days after the preliminary operation the experimental group was given Dicumarol by mouth to produce a lowered prothrombin activity. The animals in both groups were then operated upon through a new incision, the adhesions divided and the bare area estimated. The prothrombin activity of the animals in group two was kept at a low level for from four to 15 days and the animals were sacrificed eight to 21 days after lysis. The control animals were sacrificed nine to 32 days after lysis.

The animals in group three received the same preliminary operation as the other groups, but were given massive doses of Dicumarol before the gauze abrasion. With such severe depression of the prothrombin activity, hemostasis was almost impossible to obtain and no experiments regarding the reformation of adhesions were attempted. It is realized that a prothrombin activity this low would not be produced clinically. These experiments were done merely to ascertain the maximum effect one could expect from Dicumarol therapy.

Preliminary studies showed our dogs to have a normal prothrombin time of seven to eight seconds by the method of Quick.[16] The Dicumarol dosage was regulated in the same manner that it is done clinically. The initial dose was 100 mg. and additional doses of 25 to 50 mg. were given as indicated by the daily prothrombin activity. The dilution curve for prothrombin activity in the dog shows a much steeper climb at the lower percentages than does the human curve.[17] As a result, the regulation of the prothrombin level in a narrow range is very difficult. At the time these experiments were planned, it was decided to keep the prothrombin activity between 10 and 30 per cent of normal.[18] This proved all but impossible and when the results were tabulated, the range was from 7 to 60 per cent.

RESULTS

Control dogs. The total bare area after lysis of the adhesions resulting from the gauze abrasion ranged from 38.5 to 55.5 square cm. with an average of 46.2 square cm. (Table I). All of the adhesions were well formed, tough and showed no tendency to stretch. There was a preponderance of large sheet adhesions. Nine to 32 days later when the animals were sacrificed, the bare area which had reformed ranged from 68.5 to 198 square cm. with an average of 106.7 square cm. This amounts to an average reformation of 231 per cent in adhesive area. In most cases, the entire small bowel was bound firmly together in a ball. In all cases a loop or loops of small bowel were adherent to both operative incisions. In a few cases loops of bowel were adherent to the

liver, spleen, stomach or bladder. There was no gross difference in the character of number of adhesions present for nine days as contrasted to those that had been present for a longer period.

In the 12 operations performed on these animals, hemorrhage from the operative incision did not occur (Table II). There was a small superficial wound disruption in one animal.

TABLE I.—*Reformation of Adhesions*

Group	of Dogs	Average Size of Bare Area at Lysis	Average Size of Bare Area at Sacrifice	Average Percentage of Reformation of Adhesions
Control	6	46.2	106.7	231.0
Experimental	14	45.8	11.3	24.6

Experimental dogs. The adhesions resulting from the preliminary operation were equal in all respects to those found in the control group. The bare area after lysis ranged from 38 to 54.5 square cm. with an average of 45.8 square cm. This compares favorably with an average of 46.2 square cm. in the controls. As stated above, the prothrombin activity at the time of lysis and in the postoperative period ranged from 7 to 60 per cent. This level was maintained for four to 15 days postoperatively. The animals were sacrificed eight to 21 days after lysis. Hemostasis in these animals was only slightly more difficult to obtain than in the control animals.

At the time of sacrifice, the bare area ranged from 2.5 to 15 square cm. with an average of 11.3 square cm. This represents a 24.6 per cent reformation of the adhesive area as compared to the 231 per cent reformation in the

TABLE II.—*The Effect of Dicumarol on Wound Healing*

Group	Number of Operations	Hemorrhage from Incision		Wound Disruption	
		No.	Per Cent	No.	Per Cent
Control	12	0	0	1	8.3
Experimental	14	3	21.4	2	16.7
Severely dicumarolized	6	6	100.0	5	83.3

control group. Actually, the difference between the serosal areas involved, as marked as it is, by no means gives a true picture of the total gross change. The adhesions not only were smaller in size and fewer in number, but they were somewhat elastic and appeared poorly formed. Vascularization was noticeably less than in the controls. In only one instance was the small bowel adherent to the operative incision and in no instance was the spleen, liver or stomach involved. Lysis of these adhesions was more easily accomplished than in those resulting from the preliminary operation. The adhesions present in those dogs dicumarolized for only four days postoperatively seemed the same in all respects as in those animals dicumarolized for longer periods.

Slight postoperative oozing from the incision occurred in three or 21.4 per cent of these animals, but it ceased spontaneously with very little loss of blood. A minimal wound disruption occurred in two of these dogs. In each instance this was about a half inch long and extended only through the skin and subcutaneous fascia. In no instance was there disruption of the deeper layers. Aside from these two small disruptions, no difference was noted between the healing of the operative incision in this group and in the control animals.

Severely dicumarolized dogs. The prothrombin times in the animals of this group during operation and in the postoperative period ranged from 42 to 10,800 seconds or from 11 to less than 1.25 per cent prothrombin activity. Hemostasis was almost impossible to obtain and constant oozing from the operative site occurred. All of these animals died five to seven days postoperatively from hemorrhage.

At autopsy, the bare area ranged from none in one animal to 4.5 square cm. with an average of 1.4 square cm. The previously abraded area appeared to be completely healed. There were varying amounts of blood in the peritoneal cavity and all of the animals had petechiae and ecchymoses scattered throughout the muscles and viscera. Wound disruptions occurred in five or 83.3 per cent. In no case did this involve all of the layers of the abdominal wall.

DISCUSSION

The results obtained show that Dicumarol is effective in reducing the extent of postoperative adhesions under the conditions of these experiments. Allowing a large error for the inaccurate manner in which the amount of serosa involved was estimated, the difference is still marked between the results in the control and treated groups. The control animals showed an average reformation of adhesive area more than nine times that of the treated animals. In addition to this, the reformed adhesions were much tougher and more extensive. We wish to point out, however, that therapeutic doses of Dicumarol did not prevent the reformation of adhesions in a single instance. In only one case was there an absence of adhesions following treatment with Dicumarol. This result occurred in an animal that expired on the fifth postoperative day from hemorrhage after receiving massive doses of the drug.

The results obtained here agree with those reported by Lehman and Boys.[1,4,5] These authors were able to reduce the per cent of reformed adhesions from 156 in the control group of animals to 26 in the animals treated with heparin. Bloor *et al.*,[7] on the other hand, observed less than an eight per cent decrease in the likelihood of adhesion formation when heparin was used. In their experiments on the redevelopment of divided adhesions, heparinization did not decrease the incidence over that observed in the control animals. This discrepancy in results is apparently due to the fact that Lehman and Boys reported percentages which referred to the number of adhesions developing in each dog, and not to the percentage of dogs in the series in which adhesions developed. On the other hand, Bloor *et al.* placed more

stress on whether an animal did or did not develop adhesions. If the amount of peritoneal involvement in both of these series is contrasted, the discrepancy becomes more apparent than real. In Bloor's control group, the average extent of serosal involvement increased from 6.9 cm. before lysis to nine cm. after lysis—a reformation of 130.4 per cent in adhesive area. In the treated group the extent of serosal involvement decreased from eight to six cm., a reformation of adhesive area amounting to 75 per cent. Thus, treatment with heparin produced a 55.4 per cent advantage over non-treatment. We believe that this interpretation of these results is permissible if it is kept in mind that the complications accompanying adhesions are probably influenced by the number and extent of the adhesions present.

One important point mentioned previously by others[19,20] and illustrated by the work of Bloor *et al.* is that in a given group of individuals certain ones are more prone to form adhesions than others. This "adhesive diathesis"[19] makes it difficult to evaluate the effect of an agent that diminishes the number of adhesions but does not prevent them.

The available data seems to indicate that the severity but not the incidence of postoperative peritoneal adhesions in dogs can be reduced by anticoagulant therapy.

It should be stressed that this is an experimental study in dogs only and that no recommendations regarding the application of this method in human beings is intended.

CONCLUSIONS

1. The results obtained with the use of Dicumarol for the prevention of postoperative peritoneal adhesions in dogs are presented.

2. In these experiments the use of Dicumarol reduced the extent of adhesions over 200 per cent.

3. Anticoagulant therapy for four days postoperatively appears to be as effective as for longer periods of time.

4. Heparin and Dicumarol appear to be effective in decreasing, but not in preventing postoperative peritoneal adhesions in dogs.

BIBLIOGRAPHY

[1] Lehman, E. P., and F. Boys: The Prevention of Peritoneal Adhesions with Heparin. Ann. Surg., **111**: 427, 1940.

[2] *Idem:* Heparin in the Prevention of Peritoneal Adhesions. Ann. Surg., **112**: 960, 1940.

[3] *Idem:* Clinical Use of Heparin in the Peritoneum for the Prevention of Adhesions. Arch. Surg., **43**: 933, 1941.

[4] *Idem:* Experimental Prevention of Intraperitoneal Adhesions with Heparin. Surgery, **12**: 236, 1942.

[5] Boys, F., and E. P. Lehman: Experimental Studies on Peritoneal Adhesions. Ann. Surg., **118**: 612, 1943.

[6] Miki, H., and H. Santani: Heparin for the Prevention of Peritoneal Agglutination (Experimental Study). Mitt. a. d. Med. Akad. zu Kiota, **14**: 337, 1935. (Quoted by Lehman and Boys in [1] above.)

[7] Bloor, B. M., *et al.:* The Effect of Heparin upon Intra-abdominal Adhesions in Rabbits. Ann. Surg., **126**: 324, 1947.

8 Pfeiffer, D. B., and F. D. Sain: Heparin and Dicumarol—A Collective Review. Internat. Abstr. Surg., **78**: 109, 1944.

9 Allen, E. V., N. W. Barker and J. M. Waugh: A Preparation from Spoiled Sweet Clover. J. A. M. A., **120**: 1009, 1942.

10 Roderick, L. M.: A Problem in the Coagulation of the Blood, "Sweet Clover Disease of Cattle." Am. J. Physiol., **96**: 413, 1931.

11 Quick, A. J.: The Coagulation Defect in Sweet Clover Disease and in the Hemorrhagic Chick Disease of Dietary Origin. Am. J. Physiol., **118**: 260, 1937.

12 Quick, A. J.: The Anticoagulants Effective in Vivo with Special Reference to Heparin and Dicoumarol. Physiol. Rev., **24**: 297, 1944.

13 Mellanby, J.: Heparin and Blood Coagulation. Proc. Roy. Soc., London, **116**: 1, 1934.

14 Best, C. H., and N. B. Taylor: Physiological Basis of Medical Practice. Chap. on Blood Coagulation. 1939, Baltimore, Williams and Wilkins Co., 2nd Edition.

15 Crutcher, R. R., R. A. Daniel and F. T. Billings: The Effect of Sulfanilamide, Sulfathiazole, and Sulfadiazine upon the Peritoneum. Ann. Surg., **117**: 677, 1943.

16 Quick, A. J., M. Stanley-Brown and F. W. Bancroft: A Study of the Coagulation Defect in Hemophilia and in Jaundice. Am. J. M. Science, **190**: 501, 1935.

17 Conley, C. L.: Personal communication.

18 Barker, N. W.: The Clinical Use of Dicoumarol. Med. Clin. N. Am., **29**: 929, 1945.

19 Ochsner, A., and Garside, E.: Peritoneal Adhesions. Surg., Gynec. & Obst., **54**: 338, 1932.

20 Boys, F.: The Prophylaxis of Peritoneal Adhesions. Surgery, **11**: 118, 1942.

THE EFFECT OF HEPARIN ON GELATIN SPONGE HEMOSTASIS*

WM. J. GROVE, M.D., AND C. W. VERMEULEN, M.D.

CHICAGO, ILL.

FROM THE DEPARTMENT OF SURGERY, UNIVERSITY OF ILLINOIS, COLLEGE OF MEDICINE.
READ BEFORE THE FORUM ON FUNDAMENTAL SURGICAL PROBLEMS, CLINICAL CONGRESS, AMERICAN COLLEGE OF SURGEONS, LOS ANGELES, CALIFORNIA, OCTOBER 1948

Evidence has accumulated that gelatin sponge† is an effective hemostatic in wounds of parenchymatous organs and large vessels.[1, 2] In many instances the continued patency of vessels on which gelatin sponge has been used is of utmost importance. Although the incidence of thrombosis in vessels on which gelatin sponge has been used is probably no greater than those repaired by suturing, it might at times seem desirable to heparinize such patients. However, the effect of heparin upon gelatin sponge hemostasis is not known. The purpose of this investigation was to determine the effectiveness of gelatin sponge as a hemostatic agent in the presence of heparin.

METHODS

In this experiment the effect of heparin on gelatin sponge was tested in two types of wounds in 250 Gm. white rats. The first type of wound was produced by exposing a lobe of the liver under ether anesthesia. Using a razor blade a small slice of liver was removed. The denuded surface, approximately one square centimeter in size, bled profusely though other experiments have shown that this type of wound ordinarily does not result in fatal hemorrhage. The second type of wound used in this study was one of the vena cava. An incision 5 mm. long was made in the wall of the vessel in the lumbar region. Such a wound results in fatal hemorrhage if left untreated. In both the liver wound and the vena cava wound the gelatin sponge was applied after it was first soaked in saline solution. After application, firm pressure with the fingers was maintained for a period of five minutes.

Suitable control groups of animals were studied to determine the effect of such wounds left untreated with gelatin sponge. Other controls were observed when a celiotomy alone was done.

Previous experiments had shown that 10 mg. of heparin given subcutaneously in rats of the size indicated produced an incoagulable blood for longer than four hours. Therefore when heparin was given, 10 mg. were injected subcutaneously either before or 1, 24, or 48 hours following surgery.

To determine the amount of bleeding subsequent to the administration of heparin, the animals were anesthetized four hours following heparin and the abdomen opened. The site of application of the gelatin sponge plaque was inspected and the amount of bleeding into the peritoneal cavity measured. If

* Submitted for publication November, 1948.

† Gelfoam (trade name of gelatin sponge) is manufactured by the Upjohn Co.

the animal had lost one-third of its calculated blood volume, it was considered for this experiment to have had massive hemorrhage.

RESULTS

The control group of eight rats showed that when a celiotomy was done and heparin was given one hour following operation, no intraperitoneal bleeding occurred. This indicated that such hemorrhage as might be found in later experiments where the liver and vena cava were incised could not be explained as hemorrhage from the abdominal wound.

When liver wounds were produced and patched with gelatin sponge massive hemorrhage occurred in all nine animals, if heparin had been given

TABLE I.—*Results*

Type of Wound	No Gelatin Sponge		Gelatin Sponge	
	Number of Animals	% With Massive Hemorrhage	Number of Animals	% With Massive Hemorrhage
Celiotomy wound				
Heparin 1 hr. after surgery	8	0	..	..
Liver wounds				
Heparin ½ hr. *before* surgery	..	..	9	100%
Heparin 1 to 4 hrs. *after* surgery	9	89%	8	75
Heparin 24 hrs. *after* surgery	5	0	13	20
Heparin 48 hrs. *after* surgery	10	0	31	16
Vena Cava wounds				
No heparin	Immediate fatality			
Heparin 1 hr. after surgery	..	..	11	0
Heparin 24 hrs. after surgery	..	..	8	0
Heparin 48 hrs. after surgery	..	..	8	0

30 minutes before operation. This result is as expected; gelatin sponge presumably providing a substrate to strengthen a clot, will not be effective when the normal blood clotting mechanism is disturbed by large doses of heparin. If, however, the administration of heparin is delayed until after the liver wound has been produced and gelatin sponge applied, massive bleeding does not invariably occur. As expected, the longer the interval of time between operation and administration of heparin, the less is the incidence of massive secondary hemorrhage. Surprisingly enough, when heparin is given 24 or 48 hours after operation, bleeding is more likely to occur from liver wounds if gelatin sponge has been applied than if no patch of gelatin sponge was used.

When wounds of the vena cava were made the immediate application of a gelatin sponge patch was life-saving. In contradistinction to liver wounds, heparin was found safe when given as early as one hour following operation. In no animals where gelatin sponge was used and heparin given, 1, 24, or 48 hours following caval injury did massive bleeding occur. The results are summarized in the accompanying table.

DISCUSSION

It seems to be definitely demonstrated that in rats with vena cava injury a gelatin sponge patch will prevent massive hemorrhage and that heparin can be given safely within one hour of the application of the patch. Evidently, within a period of one hour the clot formed within and around the gelatin sponge is sufficiently firm and adherent to prevent bleeding even though the blood then be made uncoagulable by heparin administration.

With liver wounds of the type described, the results would indicate that bleeding may occur through and around a gelatin sponge patch if heparin is given as late as 48 hours after wounding. This can possibly be explained by assuming that bile exuding from the liver bed partially destroys or injures the previously formed clot and the slight bleeding that therefore occurs continues because the blood is now heparinized, and unable to form new clots. In such a wound the presence of gelatin sponge serves as a real impairment to healing. If the same wound is produced, but no gelatin sponge used, heparin can be given within 24 hours without subsequent bleeding; the omentum and adjacent viscera become adherent to the liver bed, sealing off the area so no bleeding occurs following heparinization.

CONCLUSIONS

1. Gelatin sponge is ineffective as an hemostatic in an already heparinized animal.

2. Animals with wounds of large vessels treated with gelatin sponge may be heparinized as early as one hour following injury without danger of hemorrhage.

BIBLIOGRAPHY

[1] Jenkins, H. P., and Rudolph Janda: Studies on the Use of Gelatin Sponge or Foam as an Hemostatic Agent in Experimental Liver Resections and Injuries to Large Veins. Ann. Surg., **124**: 952, 1946.

[2] Jampolis, R. W., H. P. Jenkins, M. M. Newman and G. L. Nardi: Control of Hemorrhage from the Cardiac Auricles by the Gelatin Sponge. Surg., **22**: 198, 1947.

SARCOIDOSIS PRODUCING PORTAL HYPERTENSION*

TREATMENT BY SPLENECTOMY AND SPLENORENAL SHUNT

ROBERT A. MINO, M.D., ARTHUR I. MURPHY, JR., M.D.
WILMINGTON, DEL.

AND

ROBERT G. LIVINGSTONE, M.D.
CAMBRIDGE, MASS.

FROM THE SURGICAL SERVICE OF DR. JAMES G. SPACKMAN, MEMORIAL HOSPITAL, WILMINGTON, DEL.

MUCH ATTENTION HAS BEEN GIVEN to veno-venous shunts in the operative treatment of portal hypertension since Blakemore and Lord perfected the nonsuture, Vitallium tube technic of blood vessel anastomosis. The recent publications of Blakemore, Whipple, Blalock, Welch, and Linton and their colleagues afford an excellent summary of the currently established indications, technics, and immediate clinical results of these procedures.

The etiologic aspects of portal hypertension have also been reviewed in these reports. Sarcoidosis of the liver, a subject which has been omitted from consideration, has apparently not been encountered as a cause of this condition.

The present communication is an account of our experience with splenectomy and splenorenal venous anastomosis in the treatment of the incapacitating symptoms of portal hypertension caused by sarcoidosis of the liver.

CASE REPORT

Mrs. E. C. (M. H. 62, 286), a Negro housewife 26 years old, was admitted to the Memorial Hospital on November 24, 1947, because of marked dyspnea and ascites. These symptoms were related to sarcoid infiltration of the liver and the spleen.

Her first admission to this hospital had occurred on November 12, 1943, three weeks after the onset of multiple joint pains, shortness of breath on slight exertion, and weakness of both legs. The details of her family history and past history were irrelevant. Her arms and legs were covered with discrete, indurated areas of pigmentation which also involved the trunk. Many shot-like lymph nodes, the largest 1 and 2 cm. in diameter, were encountered in the axillary, epitrochlear, inguinal, and femoral regions. The liver edge was palpable 8 cm. below the costal margin, and the spleen was enlarged to the level of the umbilicus. Routine examinations of the blood and of the urine disclosed no abnormalities. A chest film showed extensive, patchy lesions in the peribronchial areas, especially in both lower lobes. There were no roentgenographic changes in the bones of either hand. The presumptive diagnosis of sarcoidosis was established by histopathologic study of an excised cervical lymph node.

Trial of a variety of therapeutic measures in the out-patient department failed to prevent a gradual increase in the severity of the symptoms. Ascites was demonstrable after 18 months of treatment, and on two occasions hospitalization was required because

* Submitted for publication November, 1948. Grateful acknowledgment is made to Dr. John F. Hynes, Director of the Carpenter Memorial Tumor Clinic; to Dr. John W. Hooker, Pathologist; and to Dr. Robert W. Frelick, former Resident in Medicine, for their valuable assistance and suggestions in the treatment of this patient.

of the progressive disability which followed. Thorough clinical and laboratory studies, throughout the period of illness, indicated that the only active foci of disease were present in the spleen and liver and possibly in the spinal cord. A state of total invalidism was believed to be at hand when accentuated symptoms led to the present readmission.

Physical examination. The patient at this time was a thin young Negro woman with a strikingly enlarged, protuberant abdomen. Her weight was 135 pounds, and at the level of the umbilicus the circumference of her abdomen was 36 inches. A definite cyanosis of the nail beds was observed, and a slight degree of dyspnea was evident at rest. There were no apparent changes in the lesions of the skin or in the groups of enlarged lymph nodes which had previously been noted. The blood pressure was 110/72; the pulse rate was 88. The heart and lungs were normal. The liver edge extended to the umbilicus. The limits of the spleen were at the midline and at the left anterior superior iliac spine. There was moderate ascites. The knee and ankle jerks were absent. There was marked weakness of the extensor muscles of the thighs and lower legs, and there was moderate weakness of the other muscle groups. No peripheral edema was apparent.

Laboratory findings. The red cell count was 3,400,000, the hemoglobin level 12.5 Gm., and the white cell count, 5,000. A differential count of 71 per cent neutrophils, 23 per cent lymphocytes, 2 per cent monocytes, and 4 per cent eosinophils was noted. The coagulation time was 3½ minutes; the bleeding time was 2½ minutes. The platelet count was normal. The prothrombin time was 52 per cent of the control. The plasma protein level was 6.61 Gm. per 100 cc., representing 2.75 Gm. per 100 cc. of albumin and 3.86 Gm. per 100 cc. of globulin. With the bromsulfalein test there was 10 per cent retention in 30 minutes and 5 per cent retention in 1 hour. The cephalin cholesterol flocculation was 4 plus. The Congo red and galactose tolerance tests were negative. The concentration of the blood urea nitrogen was 20 mg. per 100 cc. The urea clearance was 113 per 100 cc. The phenolsulfonphthalein test was normal.

A complete examination of the cerebrospinal fluid revealed no abnormalities. A chest film also indicated that there had been no changes in the peribronchial lesions.

Operation. Splenectomy, with the creation of a veno-venous shunt, was recommended as the only therapeutic measure thought to offer any prospect of relief. Preliminary treatment by transfusions and by the administration of a diet low in fat and high in carbohydrate and in protein constituents was therefore instituted.

The operation was performed on December 11, 1947, (R. A. M.) with the patient under spinal and supplemental intravenous anesthesia. There was a moderate amount of clear ascitic fluid in the abdominal cavity. The visible serosal surfaces were smooth and glistening. The spleen was smooth, dark gray, and very firm to touch; it extended to the midline and to the level of the left anterior superior iliac spine. The liver was somewhat hob-nailed in appearance and also very firm to touch; its edge was at the level of the umbilicus. There were numerous retroperitoneal lymph nodes, the largest almost 3 cm. in diameter. An accessory spleen was found which was about 6 cm. in diameter. The uterus and ovaries were extremely atrophic. Moderately enlarged veins were observed in the gastrohepatic omentum and elsewhere in the portal area. The left renal vein was about 1.5 cm. in diameter, the splenic vein about 10 mm. in diameter.

The pressures in the coronary and middle colic veins were found to be equivalent to 175 mm. of saline solution.

No unusual difficulty was experienced in the removal of the spleen. The pressure in the splenic vein was subsequently found to be equivalent to 180 mm. of saline solution. In view of the appearance of the liver, the increased venous pressures were interpreted as evidence that the portal hypertension was of intrahepatic origin.

An end-to-side anastomosis of the splenic and renal veins, with preservation of the kidney, was therefore created, the presence of enlarged lymph nodes and plexuses of small blood vessels having been considered as a contraindication to the formation of a

portacaval shunt. The axial placement of a rubber-covered "McWhorter delicate model gallbladder forceps"* on the renal vein in the course of this procedure was found to be a very satisfactory method for securing partial occlusion of this vessel. The parallel closing of its very narrow blades assures an even grasp upon the vessel wall, and the flexibility of their structure results in minimal trauma to the intimal surfaces. Subsequent palpation of the anastomotic site indicated that the stoma was almost 1 cm. in diameter.

Additional determinations of the pressures were then made in various tributaries of the portal vein before the abdomen was closed. The lowest reading taken was found to be equivalent to 90 mm. of saline solution, but the accuracy of these results was considered questionable since no appreciable fluctuations of the column were associated with the respiratory movements.

The patient tolerated this procedure very well. During the operative period of approximately eight hours she received a total of 5,500 cc. of fresh citrated blood and 1,000 cc. of 5 per cent glucose in normal saline solution. She was returned to her bed with a blood pressure of 100/70 and a regular pulse rate of 110.

Postoperative course. A variety of complications developed in the postoperative period. Additional heparin was given to maintain a carefully controlled, prolonged coagulation time, but gross hematuria was noted ten hours after operation, in association with a rapidly falling blood pressure and a diminishing red cell count. The heparin was discontinued, and a total of 2,000 cc. of freshly withdrawn blood was given in the following five hours. The blood pressure was restored to normal levels by this treatment, and the subsidence of the hematuria was shortly afterwards observed. Abdominal distention in this period also made continuous gastric suction necessary. Dyspnea and cyanosis became evident 24 hours after operation. A bronchoscopic examination demonstrated an obstructing edema of the mucosa of the left lower bronchus which was attributed to the aspiration of gastric content during anesthesia. An oxygen tent afforded some relief from these symptoms. Considerable difficulty was then experienced in the management of the electrolyte balance, but with the administration of parenteral solutions a gradual return to normal was eventually observed.

A normal temperature was attained on the tenth postoperative day, and a soft solid diet, rich in protein constituents, was tolerated at this time. Fever reappeared a few days later, and in spite of massive doses of penicillin and streptomycin a subdiaphragmatic abscess developed on the left. An intravenous pyelogram demonstrated normal function and appearance of both kidneys. The abscess was incised and drained on January 17, 1948, with the patient again under spinal anesthesia. The cultures revealed strains of *Staphylococcus aureus* and *Bacillus coli* which were markedly resistant to the antibiotic agents. A superficial infection of the primary wound required drainage somewhat later, and a large decubitus ulcer finally appeared over the sacral area. This ulcer was excised on February 25, 1948, and the resulting wound was closed with a sliding flap of skin and subcutaneous tissue.

An uneventful convalescence then occurred. Healing progressed rapidly, the dyspnea and ascites disappeared, and the patient soon exhibited a ravenous appetite. The red cell count was 3,830,000, the hemoglobin level 12.5 Gm., and the white cell count 18,000. The prothrombin time was 100 per cent of the control. The plasma protein level was 6.39 Gm. per 100 cc. representing 2.45 Gm. per 100 cc. of albumin and 3.94 Gm. per 100 cc. of globulin. The cephalin cholesterol flocculation was 3 plus. With the bromsulfalein test there was 4 per cent retention in 30 minutes and no retention in 1 hour. Discharge from the hospital was granted on March 20, 1948, approximately 3½ months after operation.

Pathologic examination. The operative specimens included several retroperitoneal

* This instrument is supplied by V. Mueller and Company, Chicago.

lymph nodes, a wedge of tissue from the left lobe of the liver, the spleen, an accessory spleen, and a portion of the tail of the pancreas.

The spleen measured 28 by 18.5 by 12 cm. and weighed 2,250 Gm. (Fig. 1). There were scattered fibrinous adhesions and focal areas of hyalocapsulitis on the diaphragmatic surface of its capsule. It was abnormally firm. On section it was rusty brown in color, rubbery, and uniformly sprinkled with minute, somewhat reddish areas (Fig. 2).

FIG. 1

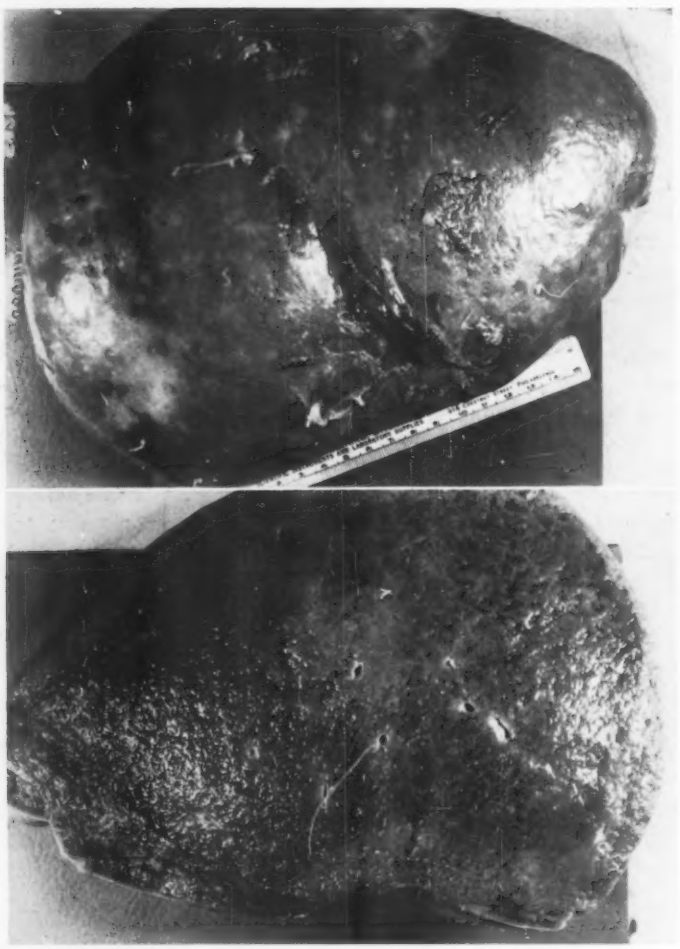


FIG. 2

FIG. 1.—The appearance of the spleen (weight 2,250 Gm.) immediately after its removal.
FIG. 2.—A cut section of the spleen.

Similar characteristics were shown by the accessory spleen.

The lesions of Boeck's sarcoid were beautifully demonstrated in the sections of the lymph nodes (Figs. 3 and 4). Definite groups of epithelioid cells were present without evidence of giant cells or of caseation necrosis.

There were also definite and extensive sarcoid lesions in the spleen (Fig. 5). Giant

cells of the Langhan's type were present, and "asteroid" inclusion bodies were occasionally noted. A fibrinoid necrosis was displayed in the central areas of many of the lesions, and in these instances a circumferential zone of partially necrotic, partially hyalinized and regenerating fibrous connective tissue was observed. There was no involvement of the intima of the veins.

FIG. 3 FIG. 4

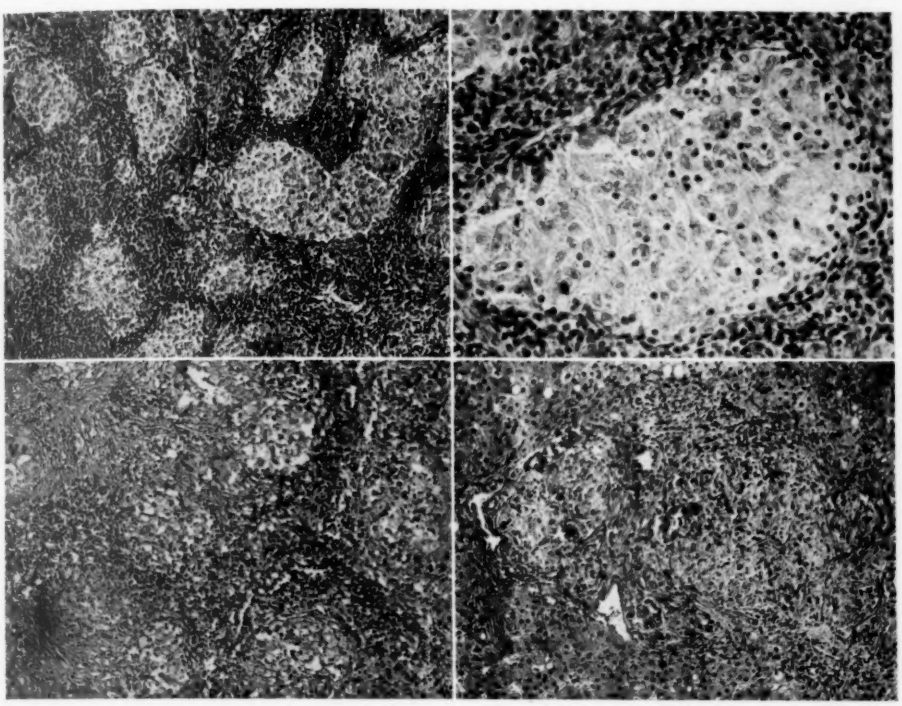


FIG. 5 FIG. 6

FIG. 3.—Sarcoid lesions in a retroperitoneal lymph node. The typical clusters of broad epithelioid cells show no evidence of giant cells or of caseation necrosis. (x 60)

FIG. 4.—Detailed view of a sarcoid lesion in a retroperitoneal lymph node. (x 175)

FIG. 5.—Sarcoid lesions in the spleen. The parenchyma is shown to be extensively involved. (x 60)

FIG. 6.—Sarcoid lesions in the liver. There is a coalescence of the lesions about the portal triad shown in the center of the field. (x 60)

The lesions in the tissue from the liver were found primarily about the tributaries of the portal vein in many of the portal triads (Fig. 6). There was occasional involvement also of the central lobular veins. A striking infiltration of the walls of several of the larger, apparently sublobular veins was evident in other sections (Fig. 7). No focal hemorrhages had occurred, although the lesions had encroached upon the intimal surfaces. A comparable infiltration has already been described by James and Wilson in the walls of the smaller splenic veins, but its occurrence in the walls of the hepatic veins is not known to have been previously reported. These findings serve to explain the mechanism of the portal hypertension in this case of sarcoidosis.

Special stains of all these tissues revealed no acidfast bacilli.

Subsequent course. The patient has exhibited a very gratifying clinical response since her discharge from the hospital. She resumed her lighter household duties a few months postoperatively. As her ravenous appetite continued, her weight soon increased to 144 pounds, but the persistence of the weakness of her legs led her to accept a somewhat restricted diet. One year after operation the red cell count was 3,500,000, the hemoglobin level 14.5 Gm., and the white cell count 14,400. The plasma protein concentration was 7.10 Gm. per 100 cc. representing 3.00 Gm. per 100 cc. albumin and 4.10 Gm. per 100 cc. globulin. The cephalin cholesterol flocculation was 4 plus. With the bromsulfalein test there was 8 per cent retention in 30 minutes and 8 per cent retention in 1 hour. A chest plate showed slight clearing of the peribronchial lesions.

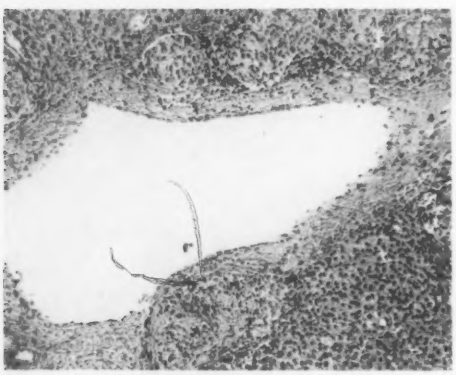


FIG. 7.—Sarcoid infiltration of the wall of a large hepatic vein. (x 60)

At the most recent visit, 18 months postoperatively, the patient weighed 130 pounds. The circumference of her abdomen was 24 inches. There was no evidence of ascites, dyspnea, or edema. The liver edge was palpable approximately 6 cm. above the umbilicus. The weakness of her legs had not been changed. The patient was noticeably alert, active, and cheerful.

COMMENT

The extensive infiltration of the spleen and liver is of special interest in this case. Nickerson, Harrell, Longcope, and Reisner have observed that involvement of these organs frequently occurs in sarcoidosis, and Nickerson and Longcope have reported that splenectomy has been performed in certain instances of this disease in the erroneous belief that the preoperative signs and symptoms were evidence of Banti's syndrome. The serious obstruction of the venous blood flow in the liver in the case recorded here is believed to be an unusual manifestation of these lesions. Their periportal distribution was undoubtedly a most important factor in the production of the ascites. The spleen is also thought to be the largest yet described in sarcoidosis.

It is evident that ascites has rarely been encountered as a complication of this disease. Reisner has described a peritoneal effusion in one case in his series, but he has attributed this finding to sarcoid infiltration of the serous membranes.

The indication for operative intervention in the case reported here was the presence of the progressive, incapacitating ascites. It is realized that sarcoidosis is a generalized disease in which the clinical manifestations vary in accord with the extent and distribution of the lesions, and it is also recognized that the occurrence of spontaneous remissions or exacerbations makes the prognosis difficult in the individual case. The patient in this instance was observed, however, for a period of four years, and, except for its progression in the spleen and liver and possibly in the spinal cord, the disease in her case was believed to have become quiescent. She was obviously being reduced to a state of invalidism, and operative treatment was thought to offer

her the only possibility of relief. The venous shunting operations are not advised in sarcoidosis unless the primary disease has become stationary and incapacitating ascites or bleeding from esophageal varices has occurred. The prognosis should be guarded in spite of operation.

SUMMARY

A case of portal hypertension which was caused by sarcoidosis of the liver is reported, and a histopathologic explanation of the mechanism of this syndrome in sarcoidosis is presented.

Treatment by splenectomy and splenorenal venous anastomosis is advised in this condition when the primary disease has entered a quiescent phase and when evidence of bleeding or of incapacitating ascites has occurred. A satisfactory result has been obtained in the case reported here 18 months postoperatively.

BIBLIOGRAPHY

1 Blakemore, A. H.: Indications for Portacaval Anastomosis—Analysis of Cases. Surg., Gynec. & Obst., **84**: 645, 1947.

2 ————: Portacaval Anastomosis. Surg., Gynec. & Obst., **87**: 270, 1948.

3 ————: The Portacaval Shunt in the Surgical Treatment of Portal Hypertension. Ann. Surg., **128**: 825, 1948.

4 Blakemore, A. H., and J. W. Lord, Jr.: A Nonsuture Method of Blood Vessel Anastomosis. Ann. Surg., **121**: 435, 1945.

5 ————: Technique of Using Vitallium Tubes in Establishing Portacaval Shunts for Portal Hypertension. Ann. Surg., **122**: 476, 1945.

6 Blalock, A.: The Use of Shunt or By-pass Operations in the Treatment of Certain Circulatory Disorders, including Portal Hypertension and Pulmonic Stenosis. Ann. Surg., **125**: 129, 1947.

7 Harrell, G. T.: Generalized Sarcoidosis of Boeck. Arch. Int. Med., **65**: 1003, 1940.

8 James I., and A. J. Wilson: Spontaneous Rupture of the Spleen in Sarcoidosis. Brit. J. Surg., **33**: 280, 1945–1946.

9 Linton, R. R.: Portacaval Shunts in the Treatment of Portal Hypertension. New England J. Med., **238**: 723, 1948.

10 Linton, R. R., I. B. Hardy, Jr., and W. Volwiler: Portacaval Shunts in the Treatment of Portal Hypertension. Surg., Gynec. & Obst., **87**: 129, 1948.

11 Linton, R. R., C. M. Jones and W. Volwiler: Portal Hypertension. Treatment by Splenectomy and Spleno-renal Anastomosis with Preservation of the Kidney. Surg. Clin. N. America, **27**: 1162, 1947.

12 Longcope, W. T.: Sarcoidosis, or Besnier-Boeck-Schaumann Disease. J. A. M. A., **117**: 1321, 1941.

13 Nickerson, S. A.: Boeck's Sarcoid: Report of Six Cases in which Autopsies Were Done. Arch. Path., **24**: 19, 1937.

14 Reisner, D.: Boeck's Sarcoid and Systemic Sarcoidosis. Am. Rev. Tuberculosis, **49**: 289 and 437, 1944.

15 Welch, C. S.: A Technique for Portacaval Anastomosis (Eck fistula). Surg., Gynec. & Obst., **85**: 492, 1947.

16 Whipple, A. O.: The Problem of Portal Hypertension in Relation to Hepatosplenopathies. Ann. Surg., **122**: 449, 1945.

OBSTRUCTION OF THE INFERIOR VENA CAVA ABOVE THE RENAL VEINS*

REPORT OF A CASE WITH RECOVERY OF RENAL FUNCTION FOLLOWING THE USE OF THE ARTIFICIAL KIDNEY

CHARLES B. RIPSTEIN, M.D., AND G. GAVIN MILLER, M.D.

MONTREAL, CANADA

FROM THE DEPARTMENT OF SURGERY, ROYAL VICTORIA HOSPITAL AND MCGILL UNIVERSITY, MONTREAL

IT HAS BEEN STATED that occlusion of the inferior vena cava above the level of the renal veins is almost universally fatal. Most of the reported human cases have been instances of sudden obstruction in a previously patent vessel. Keen[3] has pointed out that where the occlusion is gradual, adequate collateral channels can form, and although some degree of renal damage may occur, the kidney function is good enough to maintain life. Many workers have shown that ligation of the inferior vena cava above the renal veins carries a very high mortality in experimental animals.[1, 2, 6] Death occurs due to kidney failure with uremia. The renal lesion is a form of lower nephron nephrosis, the damage being chiefly in the tubules, while the glomeruli remain relatively intact.[8] This fact is important because the tubules have great powers of regeneration and if life can be maintained long enough for a collateral circulation to develop there is an excellent possibility that renal function will be restored to normal. Until recently, a patient with complete renal shutdown could survive only a limited time before death occurred due to uremia. Kolff[4] has recently developed a method of clearing the blood of toxic waste products. This machine, the "artificial kidney," utilizes the principle of dialysis across a semi-permeable membrane, and has proved its value in cases of uremia due to reversible lesions of the kidney.[6] With such an apparatus the period of survival can be indefinitely prolonged. There are no reports in the literature of its use in vena caval obstructions, but on theoretical grounds it should be of great value.

The collateral circulation in obstruction of the inferior vena cava is chiefly through the vertebral plexus, the lumbar veins and the suprarenal, testicular or ovarian veins. Other channels may develop in the anterior abdominal wall and by communications with the portal venous system. There is a greater collateral on the left side than on the right, because the embryonic channels may be present as small vessels which can enlarge if the need arises. On the right side, all the embryonic vessels have been incorporated into the vena cava and no vestigial channels are present. In addition, the testicular or ovarian vein enters the renal on the left side and offers another anastomotic pathway which is absent on the right. Thus, theoretically, the left kidney would have a better chance of developing an adequate venous return. (Fig. 1)

* Submitted for publication November, 1948.

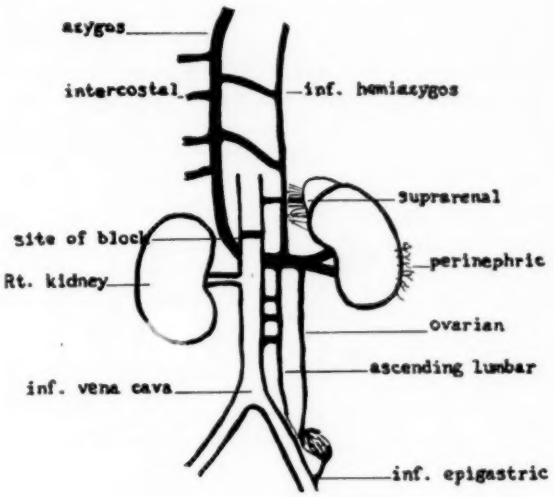


FIG. 1.—Diagram showing a greater collateral circulation may be present on the left side than on the right, because of the presence of potential embryonic channels.

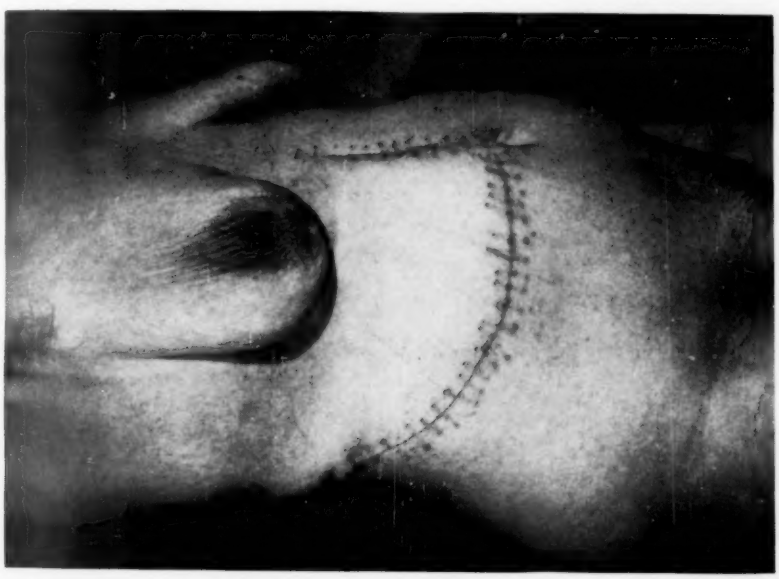


FIG. 2.—Right subcostal incision extending from the loin to the linea alba.

CASE REPORT

F. R., female age 55, was admitted to the Royal Victoria Hospital, Sept. 19, 1948, for investigation of pain in the right upper quadrant and right loin of one year's duration. Examination revealed a palpable subcostal mass and roentgen ray visualization of the gallbladder showed cholelithiasis. Laparotomy, October 28, did not confirm this diagnosis. A large retro-peritoneal tumor was found displacing the liver and gallbladder anteriorly. A biopsy was taken and the incision closed.

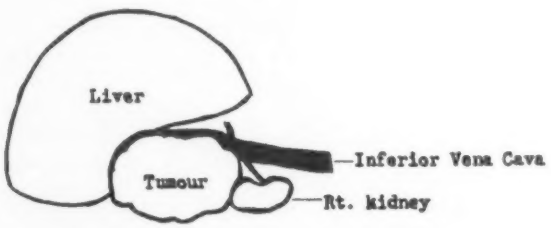


FIG. 3.—Diagram of vena cava, stretched over the surface of the growth in ribbonlike fashion, compressing the vessel to a great extent.

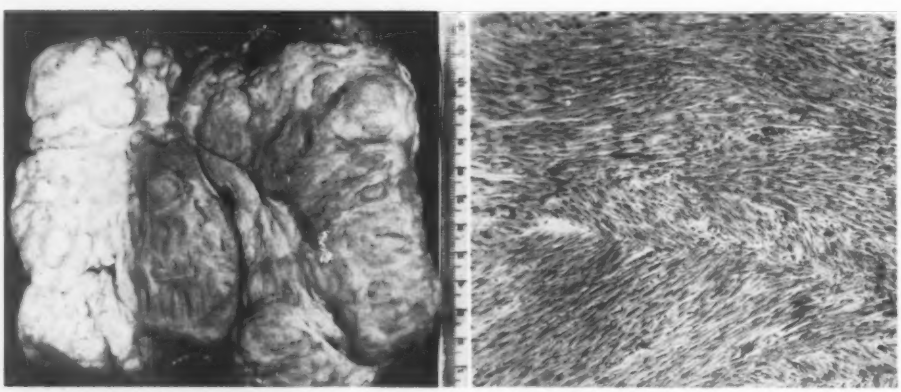


FIG. 4 FIG. 5

FIG. 4.—Gross specimen, benign fibromyoma.
FIG. 5.—Microscopic section of gross specimen.

The pathologic report established a diagnosis of benign fibromyoma, and it was decided to attempt removal of the tumor.

On Oct. 13, 1948, operation was performed through a right subcostal incision extending from the loin to the linea alba (Fig. 2). The tumor was freed from the surrounding structures and was found to be adherent to the inferior vena cava and the right kidney. The vena cava was stretched over the surface of the growth in ribbonlike fashion, compressing the vessel to a great extent (Fig. 3). The right kidney was removed, and in freeing the growth from the vena cava a segment of the vessel wall was excised. The opening was sutured with fine silk, but the lumen of the vessel was narrowed to such an extent that no

blood passed the constriction, and the vena cava was collapsed above it. The area of constriction was just above the level of the renal veins. The patient's condition was too precarious to warrant any further procedure, and it was decided to take a chance on the collateral circulation. The wound was closed with interrupted silk, and a drain inserted into the right loin (Figs. 4 and 5).

Postoperatively she recovered well from the effects of the surgical procedure but was anuric for seven days. Her NPN gradually rose to 172 mg. per 100 cc. and her creatinine

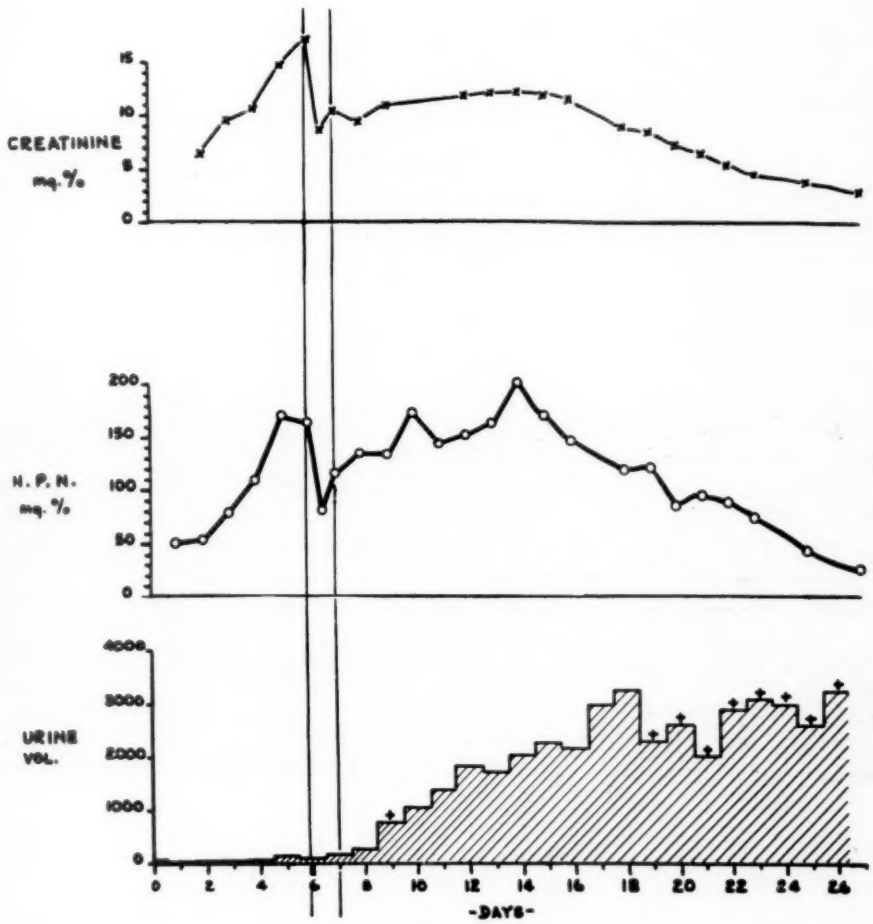


FIG. 6.—Postoperative chemical changes of blood.

to 17.2 mg. per 100 cc. On Oct. 20, 1948, she was connected to the artificial kidney and a six-hour dialysis was carried out. During the treatment the NPN dropped to 83.5 mg. per 100 cc. and the creatinine to 8.8 mg. per cc. The following day the NPN rose to 119 mg. per 100 cc. but the patient was subjectively improved and her urinary output increased to 180 cc. In the following days her urinary output gradually returned to normal. The NPN remained elevated until November 10 when it reached a normal level (Fig. 6).

Postoperative renal function tests show adequate function in the solitary kidney. The patient has moderate dependent edema of the left leg but is otherwise well.

COMMENT

This case presents several unique features. The large retro-peritoneal tumor had undoubtedly caused gradual compression of the inferior vena cava. The collateral circulation must have developed to some extent, but it was not sufficient to enable the kidney to function in the immediate postoperative period. The artificial kidney was of great value in improving the patient's condition at a critical time. The rise in NPN following dialysis has been observed in many of our previous cases. It represents a flooding of the bloodstream with waste products which have accumulated in the tissues. As a rule it is not accompanied by clinical symptoms of uremia.

During the period of anuria the blood chemistry and urine findings were typically those of a lower nephron nephrosis. The patient has apparently made a complete recovery and regained adequate kidney function.

Since the vena cava was sutured and not divided the possibility exists that some blood flow was resumed through the normal channel.

The important point is that venous occlusion existed for a period and uremia resulted. The recovery was due to the development of an adequate venous return either through collateral channels or the vena cava. Since a partial obstruction had existed for some time, it is likely that the collateral pathways were well developed.

SUMMARY

1. A case is presented in which the inferior vena cava was obstructed above the level of the renal veins.

2. After an initial period of anuria this patient regained renal function and recovered.

3. The artificial kidney was of value in combatting uremia while waiting for the collateral circulation to develop.

4. The renal lesion in vena caval obstruction is a form of lower nephron nephrosis and apparently recovery can occur under favorable circumstances.

BIBLIOGRAPHY

1 Bender, J. A., and J. H. Hayman, Jr.: Proc. Soc. Exper. Biol. & Med., **32**: 1018, 1935.
2 Chin, R.: Tr. Jap. Path. Soc., **28**: 277, 1938.
3 Keen, J. A.: Brit. J. Surg., **29**: 105, 1941.
4 Kolff, W. J.: New Ways of Treating Uremia. J. & A. Churchill Ltd., London, 1947.
5 MacLean, J. T., C. B. Ripstein, N. K. M. DeLeeuw and G. G. Miller: Canad. M. A. J., **58**: 433, 1948.
6 Northway, R. O., and R. W. Buxton: Surgery, **18**: 85, 1945.
7 Whittenberger, J. L., and C. Huggins: Arch. Surg., **41**: 1334, 1940.
8 Zuckwer, J. T.: Am. J. Path., **2**: 57, 1936.

EVACUATION OF TRAUMATIC EXTRADURAL HEMORRHAGE FROM THE POSTERIOR FOSSA*

FRANCIS C. GRANT, M.D., AND GEORGE M. AUSTIN, M.D.†

PHILADELPHIA, PA.

FROM THE DEPARTMENT OF NEUROSURGERY, HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

HEMORRHAGE of extradural origin into the posterior fossa is rarely encountered on a clinical basis. A small number of cases of this type of hemorrhage have been discovered at necropsy but clinically cured patients are few in number. A careful review of the literature has shown five previous cases of extradural posterior fossa hemorrhage with cure to be reported. The work of Wharton[6] in 1901, on 70 cases of venous sinus wounds of the brain, includes eight cases of extradural posterior fossa hemorrhage. In five of these cases, the source of bleeding was from the Torcular Herophili and in three cases the bleeding was from the lateral sinus. Only one of the cases of Torcular hemorrhage lived and none of the cases of lateral sinus hemorrhage successfully survived surgery. Gurdjian and Webster,[3] Kessel,[4] Turnbull,[5] and Coleman and Thomson,[1] have each reported one case of extradural posterior fossa hemorrhage successfully evacuated by operation. Considering the small number of cases reported and with the feeling that early recognition may aid in the successful outcome of this condition, we are adding one more case to the five previously mentioned. In the patient about to be discussed, the hemorrhage was primarily in the posterior fossa and the principal source of bleeding was from the Torcular Herophili.

CASE REPORT

R. R., a 26-year-old white male was involved in an automobile accident at approximately 3 A.M. on September 9, 1948. While driving home, he fell asleep at the wheel of his car which careened into the post of a low retaining wall. At 4 A.M. the patient walked into the local police station in a dazed condition, remembering his name but none of the details of the accident. With the exception of an abrasion in the occipital area, the patient showed no other evidence of injury. On admission to the Chestnut Hill Hospital a short time later, the blood pressure was 150/90, pulse 100, and respirations 24 per minute. The pupils were equal and reacted to light and accommodation. At the time of examination it was noted that the Babinski sign was negative bilaterally.

By 8 A.M. the blood pressure had risen to 180/100 with a pulse of 70. The patient complained of severe occipital headaches and did not appear well oriented. He responded with purposeless movements to painful stimuli and required sedation with paraldehyde at 11:45 A.M. By 2 P.M. the blood pressure had increased to 190/104 and the pulse risen to 112 per minute. There was no evidence of paralysis but the mental picture showed increasing drowsiness and confusion. It was decided that the patient's signs of increased pressure were probably on the basis of intra-cranial bleeding, and he was transferred to the Neurosurgical Service of the Hospital of the University of Pennsylvania at approximately 4:30 P.M. On admission to the University Hospital he showed pronounced stupor and it was difficult to obtain a satisfactory neurological examination. However, the left

* Submitted for publication March, 1949.

† Francis Clark Fellow in Neurosurgery.

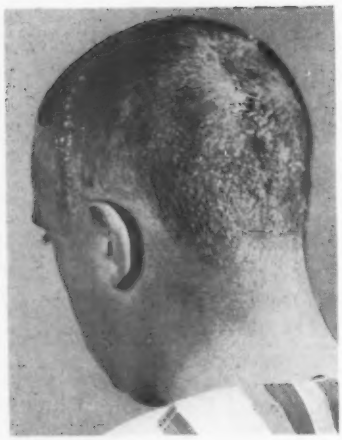


FIG. 1.—Left posterior craniotomy wound at time of discharge from hospital.

pupil appeared slightly larger than the right, there was a left VI nerve weakness and the patient showed slight evidence of a right hemiparesis. It was decided that the patient might well have an acute subdural or possibly extradural hemorrhage, and he was immediately taken to the operating room.

A left temporal burr hole was placed (G.M.A.), and showed a thin layer of blood approximately 1 mm. thick over the cortex amounting to 3 or 4 cc. of fluid. An occipital burr hole was next placed on the left side and revealed a thick extradural clot pushing the dura away for a depth of about 2 cm. In order to locate the bleeding point and evacuate the clot, a flap was turned down over the left lateral sinus, using the originally placed burr holes as limits for the anterior and posterior limbs of the flap. On turning back the flap, it became apparent that we were dealing with a large posterior fossa hemorrhage. It was primarily on the left but also present to a limited extent on the right side and had extended up over the tip of the left occipital lobe. Approximately 3 to 4 ounces of clotted and liquid blood were removed by suction and several oozing points in the lateral sinus were controlled by the Bovie current. The main source of bleeding was a

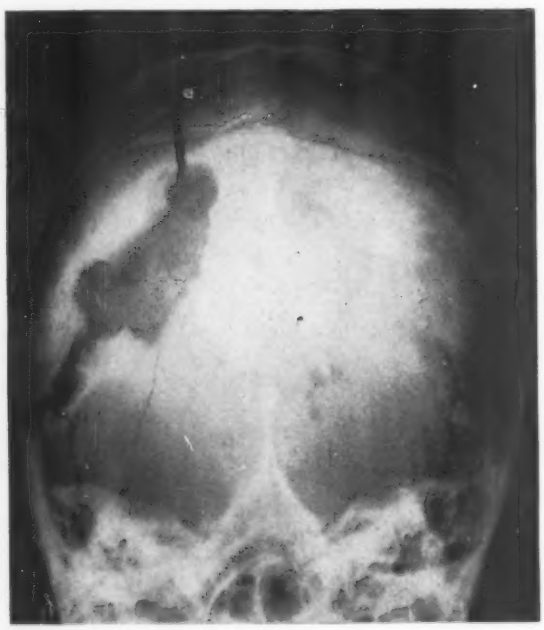


FIG. 2.—Postoperative skull film showing fracture in left occipital bone.

small tear in the Torcular Herophili. This bleeding was stopped by the use of gelfoam and the wound closed in layers. A Penrose drain was left in the posterior fossa coming out through a stab wound drainage hole posterior to the flap. At the conclusion of the procedure the patient had begun to respond although he still was not conscious enough to reply to

questions. The following morning he appeared fairly alert and was able to eat a full-sized meal. Thereafter his convalescence was uneventful. The drain was left in place for 48 hours and the patient permitted to be ambulatory on the third postoperative day. At the time of discharge from the hospital 11 days after admission, he was neurologically negative and able to return to his previous job of bartender. (Fig. 1).

Postoperative skull films on the patient showed a deep linear fracture line extending down into the occipital bone on the left side of the foramen magnum (Fig. 2).

DISCUSSION

The successful case of posterior fossa hemorrhage of extradural origin, reported by Gurdjian and Webster[3] was due to a traumatic tear in the lateral sinus. This patient straightened up after leaning forward and accidentally hit the back of his head against the sharp edge of an iron pipe, with resultant perforation of the skull. The patient became stuporous over a period of 36 hours and, at operation, an epidural hematoma of about two ounces was removed from the posterior fossa.

In Wharton's[6] series of cases, there were three instances of hemorrhage originating from the lateral sinus and bleeding into the posterior fossa, all of which proved fatal. There was one case of operation with recovery, among the five cases of Torcular hemorrhage. This case was that of a 24-year-old youth, struck on the back of the head by a dump car on August 31, 1886. The patient was brought to the Hospital of the University of Pennsylvania and found to have sustained a compound fracture of the occipital bone. The skull was trephined and the depressed fracture elevated by Professor Ashhurst. When the largest fragment was removed, "just over the junction of the lateral and superior longitudinal sinuses, there was a gush of venous blood which was quickly controlled by packing the wound with antiseptic gauze." The patient recovered, and five months later was readmitted to the University Hospital with typhoid fever which proved fatal. Necropsy showed a well organized thrombus over the Torcular.

These two cases, reported by Gurdjian and Webster[3] and Wharton,[6] have two points in common. They were both cases of acute hemorrhage and they were both due to a torn sinus following depressed skull fracture.

The case of Coleman and Thomson[1] was that of a nine-year-old child who fell and suffered mild trauma to the back of the head without unconsciousness. Roentgenograms of the skull showed a midline linear fracture extending into the rim of the foramen magnum. Approximately 60 hours after the trauma the child was hypotonic and areflexic. At operation a bilateral extradural cerebellar clot was removed, followed by complete recovery.

Turnbull[5] described an interesting case of chronic extradural cerebellar hematoma. The patient suffered a fall on the ice with a resultant blow to the left forehead, ten months prior to coming to surgery. Roentgenograms of the skull revealed no evidence of fracture. However, she showed pronounced cerebellar signs and a ventriculogram revealed a moderate internal hydrocephalus. At operation, a hematoma, the size of a golf ball was found over

the right cerebellar hemisphere. The patient made an uneventful postoperative recovery.

Kessel[4] has described the case of a 24-year-old girl who fell from a bicycle striking the back of her head. A roentgenogram of the skull revealed no fracture but the left half of the lambdoid suture showed separation. No cerebellar signs were noted but the patient had three tonic seizures in the 60-hour period following admission and preceding surgery. At operation a large extradural clot was removed from over the left cerebellar hemisphere. This was followed by gradual but complete recovery.

These cases all reveal slightly varying etiology, but the type of roentgen-ray picture may be divided into three groups. The cases of Turnbull[5] and Kessel[4] showed no fracture at all, but Kessel's showed a slight separation of the left half of the lambdoid suture. Wharton's[6] case, and that of Gurdjian and Webster,[3] both revealed compound depressed fractures. In our own case, and that of Coleman and Thomson,[1] simple linear fractures were found to run down toward the foramen magnum.

Likewise, the neurological picture varied considerably, and only two patients showed signs of cerebellar involvement when examined preoperatively. There are a number of fatal cases reported, in which the traumatic instrument itself, such as a bullet, icepick, etc., actually produced the tear in the dural sinus following perforation of the bone. However, none of those occurring into the posterior fossa has recovered.

Most recently, Gordy[2] has again stressed the importance of attaching localizing significance to overlying superficial scalp abrasions following mild head trauma. Certainly the case we have just reported presented a mild scalp abrasion over the occiput which was not considered significant at time of examination. This is of increasing importance when it is realized that there may or may not be suggestive roentgen-ray evidence for this type of lesion and that cerebellar signs are only occasionally present.

BIBLIOGRAPHY

1 Coleman, C. C., and J. L. Thomson: Extradural Hemorrhage in the Posterior Fossa. Surgery, **10**: 985–990, 1941.

2 Gordy, P. D.: Extradural Hemorrhage of the Anterior and Posterior Fossa. J. Neurosurgery, **5**: 294–298, 1948.

3 Gurdjian, E. S., and J. E. Webster: Extradural Hemorrhage. International Abstract of Surgery, **75**: 206–220, 1942.

4 Kessel, F. K.: Cerebellar Extradural Hematoma. J. Neurol. & Psychiat., **5**: 96–100, 1942.

5 Turnbull, F.: Extradural Cerebellar Hematoma. A Case Report. J. Neurosurg., **1**: 321–324, 1944.

6 Wharton, H. R.: Wounds of the Venous Sinuses of the Brain. ANNALS OF SURGERY, **34**: 81–108, 1901.

MASCULINIZING TUMOR OF THE OVARY*

DAVID KERSHNER, M.D., MENDEL JACOBI, M.D., F.A.C.P., AND LEON N. KESSLER, M.D.

BROOKLYN, N. Y.

MASCULINIZING TUMORS OF THE OVARY are admittedly rare. These generally fall into two main groups: arrhenoblastoma, and a heterogeneous group classified as "virilizing lipoid cell tumors" by Barzilai.[3] The first case of arrhenoblastoma was reported by Pick[20] in 1905, and it was not until 1933 that a case was reported as such in America.[23] However, in 1921 Moots[15] described a 27-year-old patient with "lateral partial glandular hermaphroditism." This woman was masculinized and had a tumor of the left ovary. When the "fibroblastic sarcoma of embryonic testis" of the left ovary was removed, she became refeminized. The microscopy as described, and the clinical picture designate this as an arrhenoblastoma. Baldwin and Gafford[1] in 1936 reviewed the literature and could find only 33 cases. The most recent review, that of Iverson[8] brings the total to 94 cases. The total number of "virilizing lipoid cell tumors" recorded in the world literature is 21; these, too, are summarized by Iverson.[8]

While the pathologic diagnosis of arrhenoblastoma based on histologic study has occasioned little difficulty in the past (Iverson[8]), the case to be reported indicates that this need not be and is indeed not always so. The chief function of this paper, apart from adding a new case to the literature, is to emphasize the difficulty in making a diagnosis, especially when this diagnosis is based solely on histologic examination of the tumor.

CASE REPORT

Mrs. M. S., a 34-year-old white Polish woman, was first seen at home late at night on November 23, 1943. She complained of abdominal pain, and this was her first such attack. The pain, centered in the left lower abdominal quadrant, had come on suddenly, and was of several hours duration. There had been no nausea or vomiting, nor had the patient had any bowel disturbances; urination had not been excessively frequent. Menstruation had been normal and regular, but had ceased suddenly two years previously. For several years she had had normal cohabitation, but had not conceived. She had two normal children, 18 and 14 years of age, both living, and had had one spontaneous miscarriage prior to the birth of her first child.

On examination, temperature, pulse and respiration were normal. The patient was a robust woman physically; her head and neck and chest were negative. Her abdomen was moderately tender and in the left lower quadrant there was a palpable tender mass about the size of a large orange. Bimanual examination revealed that this mass was attached to the left adnexae; the right adnexae appeared normal; the cervix was not tender to touch, nor was the uterus enlarged. A diagnosis of ovarian cyst with probable twisted pedicle was made. Hospitalization was advised, but was refused.

* Submitted for publication March, 1949.

The following morning the pain was more severe and the patient was admitted to the Beth-El Hospital. She now appeared to be acutely ill. The abdominal pain was more generalized; there was more resistance to palpation, and the cyst could not be felt as distinctly. Temperature was 100°; pulse 94; respiration 20; and blood pressure 125/80. Her red and white cell counts were 4,200,000 and 12,000 respectively, with 68 per cent polymorphonuclear leucocytes and 22 per cent lymphocytes; hemoglobin was 85 per cent. Her urine had a specific gravity of 1.020, was yellow in color, showed no casts, a few epithelial cells and a few white cells, and was negative for both albumin and sugar.

She was operated upon under spinal anesthesia with the preoperative diagnosis of a left ovarian cyst with twisted pedicle. When the peritoneal cavity was opened, a bloody fluid in which floated clumps of granular reddish-gray neoplastic tissue was observed. The left ovary had been replaced by a cystic mass approximately 10 cm. in diameter which had perforated. There was no walling off and no matting. The pelvic region was filled with this bloody fluid. The uterus appeared smaller than usual, almost infantile, and the right ovary was shrunken and firm. Both tubes and ovaries were removed and the fluid aspirated from the peritoneal cavity. The abdomen was closed in layers. The patient had a normal uneventful postoperative course. The wound healed well and she was discharged on the tenth postoperative day. Several days after the operation, the microscopic slides were examined and the diagnosis of arrhenoblastoma was made (M. J.).

On the basis of this new information the patient and her husband were carefully questioned and the patient was re-examined. The following additional data was obtained. As indicated above, the patient had stopped menstruating two years previously; she had not conceived for many years despite the fact that no contraceptives had been used. Sex life had been otherwise normal and there had been no change in libido. The patient had always been strong and robust and no change had been noted in that regard. However, her voice had changed; it had become deeper and husky; she had also become more hairy. Examination revealed no marked hirsutism; there were sparse hairs on her upper lip; the pubic hair, however, was definitely of the male type, straight and coarse and extending to the umbilicus; the legs and arms felt firm; the hips were narrow and lacked female contour; her breasts were small, flat, and devoid of fat; the labia majora appeared small; the clitoris, on the other hand, was enlarged and firm. A clear cut defeminization had apparently occurred.

Because of the widespread intraperitoneal dissemination of neoplastic tissue when the mass ruptured, we suggested postoperative radiation therapy. The patient refused such therapy or any other medication.

More than five years have now elapsed since the operation. She feels well and has no complaints. Together with her son, she operates a 104-acre farm. She had gained about 40 pounds in weight but during the past two years since working on the farm she lost about 25 pounds. Her libido is unchanged and sex life has continued normally. Physically there appears to be a distinct refeminization. Her voice is softer. Her breasts became rounded, firm and prominent, but in the past year have become pendulous. The pubic hair is now curly and there is less hair above the pubis. There is no hair on the face. The clitoris is much smaller and softer.

PATHOLOGIC REPORT (M.J.)

The specimen was composed of a mass approximately 7 cm. in diameter which was almost completely filled with a very friable grayish tissue and considerable recent blood clot. There were several irregular rents. The outer surface was smooth, glistening and felt firm. Attached to it was a fallopian tube 5 cm. long, patent and grossly unaltered. The smaller ovary appeared atrophic when compared with the tube, although there were no apparent gross fibrous changes; the surface was smooth. On section corpora albicantia were distinct and no cysts were observable.

MICROSCOPIC DESCRIPTION

Sections of the smaller ovary showed no histologic changes. These contained numerous corpora albicantia, but no corpora lutea, cysts or hemorrhagic areas; nor were any fragments of luteum-like cells present. Both tubes were histologically unaltered.

Sections of the mass and of the loose tissue accompanying the specimen showed a rather narrowed but highly cellular structure which appeared to be of three main types. In all of these, however, the basic cell was round or cuboidal or low columnar and small. All had rather large, central or slightly eccentric, rounded vesicular nuclei. These cells were arranged in short or long solid cords surrounded by rather cellular (spindle cell) or mod-

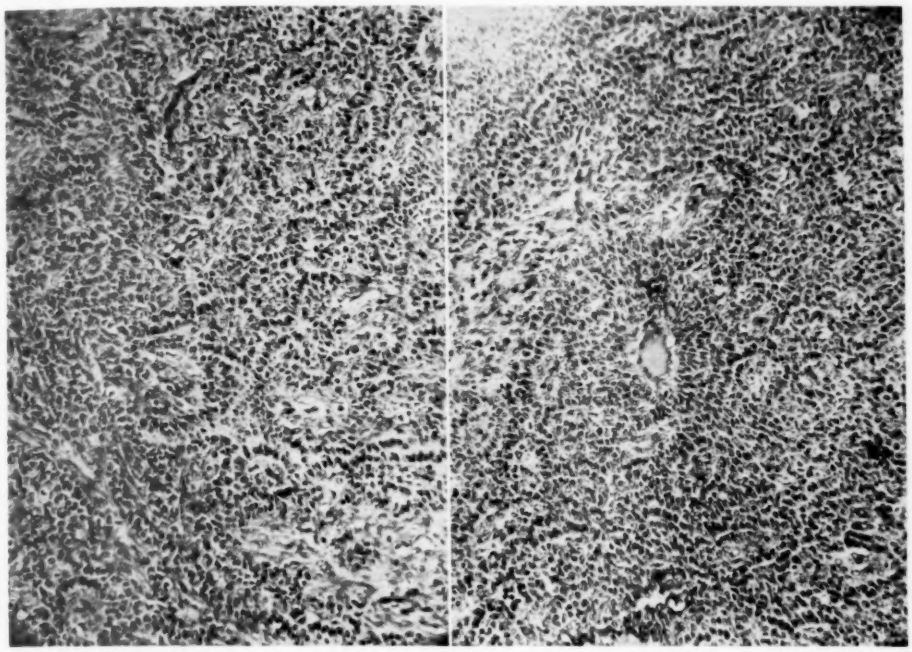


FIG. 1 FIG. 2

FIG. 1.—Low power photomicrograph of tumor showing tubular structures resembling testicular tumors.

FIG. 2.—Low power photomicrograph showing anaplastic and spindle arrangement of cells, and an area resembling the so-called Call-Exner body.

erately adult fibrous tissue; in numerous places distinct tubular patterns with well developed tubules lined by cuboidal or columnar cells with basally-polarized nuclei interspersed these cords. This tissue was rather sharply demarcated from the very small amount of fibrous ovarian tissue (stroma) surrounding it; here and there, however, the neoplastic cells extended almost to the capsular surface. There was considerable necrosis in the deeper portions of the tumor, with recent hemorrhage; scattered between the tumor and the surrounding ovarian stroma were present clumps of old blood pigment and some phagocytes. In a few places one found small cystic folliclelike structures containing homogeneous acidic substance and somewhat reminiscent of the so-called Call-Exner bodies seen in the mature granulosa portion of the graafian follicle. No other follicular elements were present nor were the surrounding tumor cells as definitely arranged in such areas as is noted in instances

of granulosa cell tumor. These areas were interpreted as being accidental features due to tumor degeneration. Scattered sparsely through the sections were isolated large vacuolated cells, suggestively lipoid-containing; these cells very occasionally occurred in small clusters. Numerous sections from various portions of the tumor failed to disclose any cytologic or histologic elements other than those noted above. There was no suggestion of any teratomatous elements. The structures described above are shown in the accompanying photomicrographs (Figs. 1–6). On the basis of the gross and microscopic findings the mass was diagnosed as an arrhenoblastoma.

DISCUSSION

Although the slides described above were seen by several pathologists in this city, no questions as to classification as an arrhenoblastoma were raised.

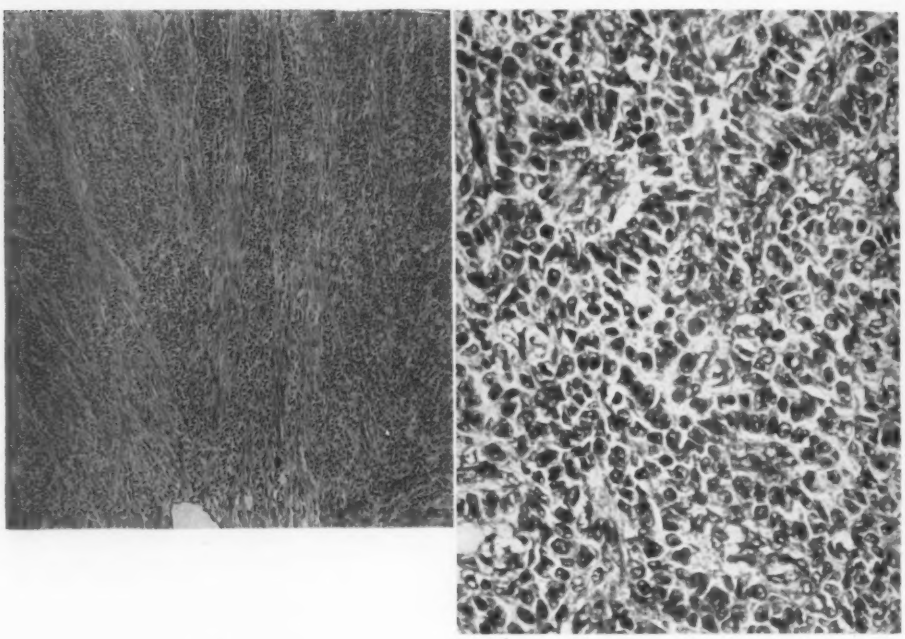


FIG. 3 FIG. 4

FIG. 3.—Low power photomicrograph showing intermediate stages between Fig. 1 and Fig. 2. Section contains a large amount of stroma.
FIG. 4.—High power photomicrograph of tumor through the tubular area.

Then Dr. Nathan Mitchell, our (M.J.) successor as pathologist at the Beth-El Hospital, in a routine examination of the hospital files, suggested that the tumor was of the granulosa cell variety. The slides had previously been carefully studied by Doctors Paul Klemperer[9] and Sadao Otani[19] of Mt. Sinai Hospital, New York, and by Dr. Herman Bolker,[5] pathologist to the Brooklyn Cancer Hospital. All three had concurred in the diagnosis of arrhenoblastoma. Dr. Klemperer and Dr. Otani suggested, on the basis of a case of their own, that the tumor be studied further for evidences of teratomatous

growth. As indicated above, no such elements were found upon very exhaustive examination.

In view of the opinion of Dr. Mitchell, to which he adhered on morphologic grounds even after being made aware of the clinical picture, slides were submitted to a prominent tumor pathologist who thought that the tumor was granulosa in type. This pathologist has recently again studied the slides with full knowledge of the subsequent opinions. He still adheres to his original diagnosis of granulosa cell tumor, and requests that his name not be published.

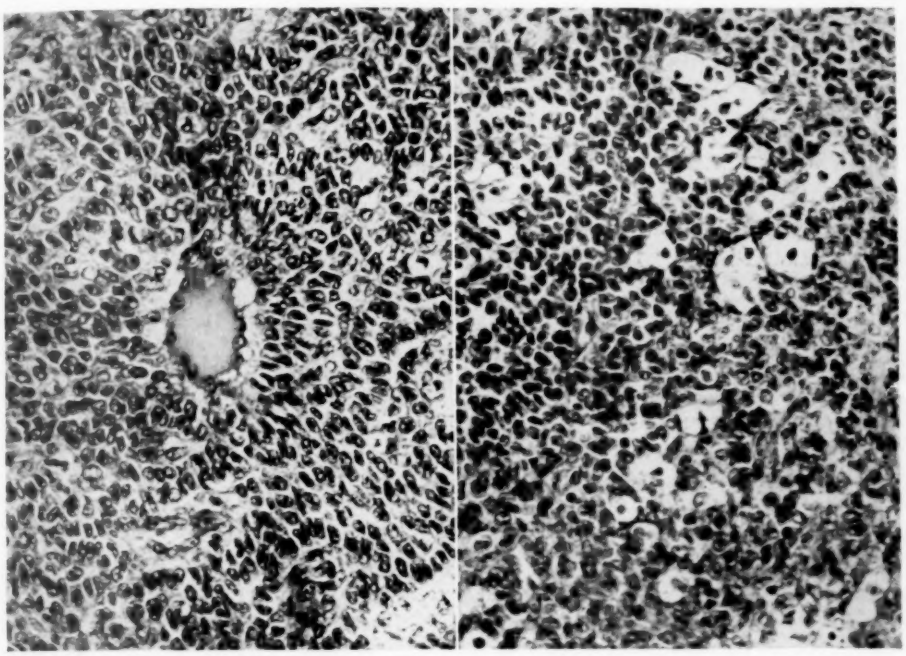


FIG. 5 FIG. 6

FIG. 5.—High power photomicrograph of the tumor through the anaplastic and spindle cell areas. Note the absence of palisade cellular arrangement around the homogeneous material in the area suggesting the so-called Call-Exner body and the degenerative features of cells in the vicinity.

FIG. 6.—High power microphotograph of the tumor showing the generally discrete lipoid-like cells. Note total absence of lutein-body formation.

He suggested that the opinion of Dr. Andrew Marchetti, then of Cornell University Medical College, be sought. Dr. Marchetti[12] unequivocally classified the tumor as an arrhenoblastoma.

The slides were then sent to Dr. Robert Meyer[13] who said: "This is a clear granulosa cell tumor, so called labyrinthine type." No reasons for this opinion were advanced. Dr. Meyer is credited with having originated the term "arrhenoblastoma" from the Greek "arrhenas," which means "male"; postulating that the tumor arises from cords of male cells persisting in the medullary portion of the ovary from early gonadogenesis, they having failed for some

reason to undergo the normal process of atrophy. The slides were then examined by Dr. Emil Novak, who concurred in the diagnosis of granulosa cell tumor, stating[16] "not only the morphology of the cells, but also their arrangement in little clusters, suggesting primitive follicles, as well as the presence of Call-Exner bodies, would leave no doubt of the diagnosis. The cylindromatous tendency is very marked in some areas, so that the cells are reduced to long thin columns which suggest arrhenoblastoma, but pictures of this type are not unusual with granulosa cell tumor. I do not see any evidence of arrhenoblastoma in this section, in spite of the fact that the history indicates a definite masculinization." With this latter statement, Dr. Novak was probably referring to page 417 of his monograph on Obstetric and Gynecologic Pathology[17] where he says, "The fact remains, however, that the clinical history is of the greatest value to the pathologist in the microscopical examination of these tumors."

Two years later, Dr. Novak asked for further data in this case, which had been restudied and was now classified as an arrhenoblastoma. In reply to a query from Dr. Mitchell, Dr. Novak said, "I can only say that further study of these slides by all the members of the Ovarian Tumor Committee (of the Registry of Ovarian Tumors of the American Gynecological Society) led to the diagnosis of arrhenoblastoma, which of course matches up very well with the clinical history of the case. It may seem strange that there should be any difficulty in distinguishing between granulosa cell tumor and arrhenoblastoma, but the fact is that there are certain cases in which the histologic picture is almost identical in many areas. As a matter of fact, one of the members of our committee felt that this tumor would better be considered a gynandroblastoma in which both types of tissue are present, although the effects are practically always masculinizing. However, we have definitely classified this tumor in our Registry as an arrhenoblastoma."[18]

These diverse opinions on identical material recall the experience of Cole[6] with tumors of the stomach, pointing up the profound limitations of morphology. These should make the clinician wary of regarding the pathologic-morphologic diagnosis as an absolute yardstick, and should raise serious questions as to the malignancy of tumors classified by such criteria, particularly in a group which is still so small. Thus, though our case showed evidence of peritoneal implants at the operating table, and the histology suggested malignant characteristics, more than five years have now elapsed without the slightest suggestion of cancer, this despite the absence of any additional therapy designed to hold a malignant tumor in check. Others have had similar experiences with so-called malignant ovarian tumors.[11] The implication of those concurring in the diagnosis of granulosa cell tumor is that this type of tumor may be associated with masculinizing changes. As pointed out by Seyle[22] such a combination is exceptional. When this combination does exist, a very small arrhenoblastomatous area occurring in a tumor otherwise predominantly granulosa cell in character may give rise to virilization. This could only be detected by serial sectioning and examination of the entire tumor, a pro-

cedure not generally carried out in cases so reported. In addition, in such a case the masculinizing features do not ordinarily subside after ablation of the tumor as they characteristically do in instances of arrhenoblastoma.[21] Whenever virilizing changes occur with granulosa cell tumor, the "granulosa cells" either become thoroughly luteinized, in many instances to the point of resembling corpora lutea (Novak,[17] page 402) or show large masses of lipoid cells in the interstitial stroma. It has been postulated by Novak and by Iverson, that masculinization is a function of these lipotropic cells. While vacuolated lipoid containing cells were found in the stroma in our case, the so-called granulosa cells did not show lipotropic changes. In addition, although the masculinizing features in our patient were rather prominent and receded after the removal of the tumor, the stromal lipotropic cells were relatively few in number, inconspicuous, discrete and never in masses of lutein or adrenal-like character. The so-called Call-Exner bodies in our material we interpret as evidence of degeneration of the tumor tissue; no unequivocal follicles were found. As pointed out by Ewing,[7] "In a substantial proportion of ovarian tumors as they actually occur, the diagnosis is largely a matter of arbitrary decision on the part of the observer." If this is so, in the present state of our knowledge, we prefer, for reasons of simplicity and clarity, to adopt the nomenclature of Burrows,[2] who designates as "arrhenoma" all testoid producing, and as "theeloma" all folliculoid producing tumors, irrespective of their structure, especially in view of the statement of Seyle that "it is impossible with the histologic methods now available, to determine the origin of these tumors with certainty."

Iverson's study, pointing out that masculinizing tumors may arise from totipotential ovarian elements, as well as the diversity of classification of these tumors by competent pathologists based on what may be minor and perhaps inconsequential differences in morphology, indicates that further knowledge in this field will come about only when the clinician preoperatively becomes more conscious of these tumors. More detailed studies of the patient's hormonal physiology, and of the hormonal content of the tumor proper, as has been done in instances of testicular tumor by Beilly, Kurland, and Jacobi,[4] should be undertaken. Kanter and Klawans[10] studied the electrolyte and nitrogenous bodies in the urine and in the blood, and also made hormonal determinations in the urine and on parts of the tumor in a case of arrhenoblastoma; but thus far there have been few clinical studies of hormonal physiology in connection with masculinizing tumors of the ovary.

SUMMARY

1. A case of masculinizing tumor of the ovary is reported. Despite rupture into the peritoneal cavity with consequent dissemination of neoplastic material, the patient, after removal of the mass, has remained free of untoward symptoms for more than five years, with no additional medication. Refeminization has also occurred.

2. The difficulties of pathologic classification on morphologic ground alone are discussed with reference to this specific case. A plea is made for a greater awareness of these tumors preoperatively, which, in turn, may lead to more numerous and detailed study of the hormonal physiology of the patient. It is also suggested that the tumor itself be assayed hormonally in order to arrive at a better correlation of clinical findings, hormonal physiology and pathologic anatomy.

BIBLIOGRAPHY

1 Baldwin, L. G., and J. A. Gafford, Jr.: Endocrinology, **20**: 373, 1936.
2 Burrows, H., Jr.: Obst. & Gynec., Brit. Emp., **50**: 430, 1943.
3 Barzilai, G.: Atlas of Ovarian Tumors. 1943, New York, Grune & Stratton.
4 Beilly, J., I. Kurland and M. Jacobi, Jr.: Endocrinology, **26**: 965, 1940.
5 Bolker, H.: Personal communication, November, 1943.
6 Cole, L. G.: Surg., Gynec. & Obst., **63**: 689, 1936.
7 Ewing, J.: Neoplastic Diseases. 1928, Philadelphia, W. B. Saunders Co.
8 Iverson, L.: Surg., Gynec. & Obst., **84**: 213, 1947.
9 Klemperer, P.: Personal communication, March, 1946.
10 Kanter, A. E., and A. H. Klawans: Amer. J. Cancer, **40**: 474, 1940.
11 Levine, W., and S. Weiner: Amer. Jr. Obst. & Gynec., **49**: 778, 1945.
12 Marchetti, A. A.: Personal communication, December, 1946.
13 Meyer, R.: Personal communication, January, 1947.
14 ————: Amer. J. Obst. & Gynec., **22**: 697, 1931.
15 Moots, C. W.: Amer. J. Obst. & Gynec., **1**: 864, 1921.
16 Novak, E.: Personal communication, January, 1947.
17 ————: Gynecological & Obstetrical Pathology, 1947, Philadelphia, W. B. Saunders Co.
18 ————: Personal communication, July, 1948.
19 Otani, S.: Personal communication, March, 1946.
20 Pick, L.: Ber. Klin. Wchn., **42**: 502, 1905.
21 Robinson, M. R.: Am. J. Obst. & Gynec., **5**: 581, 1923.
22 Seyle, H.: Encycl. Endocrinology, Sect. IV, Vol. VII. 75–82, Richardson, Bond, and Wright.
23 Taylor, J. M., S. J. Wolferman and T. Kroch: Surg., Gynec. & Obst., **56**: 1040, 1933.

EDITORIAL ADDRESS

Original typed manuscripts and illustrations submitted to this Journal should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY.

John H. Gibbon, Jr., M.D.

1025 Walnut Street, Philadelphia 7, Pa.

Contributions in a foreign language when accepted will be translated and published in English.

Exchanges and Books for Review should be sent to Dr. Gibbon at the above address.

Subscriptions, advertising and all business communications should be addressed

ANNALS OF SURGERY

East Washington Square, Philadelphia 5, Pa.

APPENDICEAL CALCULI; THEIR PATHOLOGIC AND CLINICAL SIGNIFICANCE*

ROBERT I. LOWENBERG, M.D.

NEW HAVEN, CONN.

Although fecal concretions are commonly found within the appendix, calculi are quite unusual. Bunch and Adcock[1] found only one in 2,000 appendices. The rarity of this disease and its clinical significance justify reporting an additional case. Moreover, the diagnosis in this case was made preoperatively.

CASE HISTORY

R. W. S., a 21-year-old white male, entered the hospital on January 12, 1948, with the chief complaint of pain in the right lower quadrant of the abdomen of two weeks' duration. Following discharge from the Army in April, 1947, he lost 23 pounds. Two weeks prior to admission the patient had intermittent attacks of right lower quadrant pain lasting a few hours at a time. The pain was dull, non-radiating, and unrelated to meals, defecation, or urination. Past and family history were non-contributory.

Physical examination revealed a thin, sluggish patient. His temperature was 98 degrees F., pulse 80, and his respiratory rate 20. The abdomen was scaphoid, soft, and slightly tender to deep palpation over McBurney's point, but rebound tenderness was not elicited. Rectal examination was negative.

Laboratory studies revealed a white-cell count of 4,100, with 43 per cent neutrophils, 53 per cent lymphocytes, 2 per cent monocytes, and 2 per cent eosinophils. The red-cell count was 4,100,000 with 14.0 Gm. of hemoglobin. The urinary sediment contained occasional erythrocytes and granular casts. The urine culture was negative. Typhoid and paratyphoid agglutinations were negative.

Roentgen ray examination of the chest was within normal limits. Barium enema films showed partial filling of the appendix and calculi in the right lower quadrant. Retrograde pyelography revealed a normal urinary tract. The roentgenologic diagnosis was "chronic (stasis) appendix."

On January 19, 1948, an axillary lymph node was removed under local anesthesia. The pathologic report was lymphoid hyperplasia. At laparotomy five days later, the appendix was found lying over the pelvic brim, non-adherent to the adjacent structures. Palpation revealed that it contained several stones, including a large one near its base. Appendectomy was performed after a thorough exploration failed to reveal any other abnormalities. The postoperative course was uneventful. He was free of abdominal pain and had gained six pounds when seen eight months later.

The pathologic report indicated that the appendix was 8 cm. long and varied from 1.5 to 3.7 cm. in width, with a dilatation a short distance from its base. Within the appendix were seven calculi, the largest one being 2.5 by 2.0 by 1.6 cm. This stone was roughly cuboidal in shape with several nodular projections on its surface. The other stones varied in size and shape. The mucosal surface of the appendix was slightly edematous and grey with pinkish discoloration. The wall was thickened and there was

* Lecturer in Anatomy, Yale University School of Medicine; former Chief Resident, Veterans Administration Hospital, Newington, Conn. Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the author. Submitted for publication April, 1949.

congestion of the serosal vessels. Microscopically the mucosal glands were intact. The submucosa was replaced by dense fibers of collagenous connective tissue which had encircled the lymphoid follicles and obliterated the inner layer of the muscularis. The pathologic diagnoses were appendiceal calculi and chronic healed appendicitis.

Comment. The giant calculus in this case measured 8.0 cc., the fourth largest reported in the literature. A complete tabulation of the reported cases is shown in Table I.

TABLE I.—*Appendiceal Calculi Reported in the Literature Indicating the Size of the Individual Stones and the Eventual Outcome of the Pathologic Process in Each Instance.*

	Dimensions	Volume	Number of Calculi	Perforation	Size of Appendix
Tripodi and Kruger[17]	2.5 cm. diameter	8.2 cm.	1	No	5 x 2.5 cm.
Thomas[7]	3 x 1.5 cm.	...	1	Yes	
Pilcher[18]	2.75 cm. diameter	10.8	1	No	6.5 x 3.3
Bunch and Adcock[1]	2.70 cm. diameter	10.2	5	No	3.5 x 1.4
Packard[19]	A. 2.4 x 1	8	2	Yes	7.0 x 1.5
	B. 1.5 x 0.6				
Shahan[20]	1 x 0.7	...	23	No	
Jackman[16]	A. 0.8 x 3.14	...	1	Yes	
	B. 0.5 x 3.14	...	1	Yes	
Guido[21]	1 x 2 x 2.5	5.0	1	No	
Shelley[22]	Boomerang-shaped, small	...	1	Yes	8 x 3 cm.
Vermooten[9]	2 x 1 x 1.5	3.0	4	Yes	7 x 3.5
Mulleder[23]	4.5 x 1.5				
Rigollot-Simonnot, and Saissi[24]	3 x 1.8				
Jacobs[25]	2.5 x 3	...	..	Yes	
Douglas and Le Wald[14]	A. 2 x 1.5	...	1	Yes	
	B. 1.6 x 1.2	...	1	Yes	
Wells[13]	3.25 x 0.25	...	3	Yes	
Downes[26]	Filbert sized				
Levi[27]	.....	...	1	No	
Albert[10]	.....	...	4	No	
Lowenberg	2.5 x 2.0 x 1.6	8.0	7	No	8 x 2.7 cm.

Pathologic Physiology. Appendicitis may be due primarily to inflammatory change or to mechanical factors. Appendicopathy of the mechanical type may be initiated by any of the following foreign bodies: "shot, pins, glass, eggshell, enamel, bristles, hair, wood, gallstones, pin worms, cherry stones, grape seeds, raspberry seeds, caraway seeds, fig seeds, etc.,"[2] bilharzia,[3] and clam shells.[4] Any of these may form the nucleus of a fecalith or a calculus.

When a bolus of feces becomes impacted within the appendix, calcium salts from the mucous glands in the crypts of Lieberkühn may be deposited upon the concretion. The appendix becomes thickened and the stone laminated by repetition of this process.[5] If there is interference with circulation or lymphatic drainage of the appendiceal wall during any of these episodes perforation may occur.[6] In nine of the 17 cases reviewed perforation took place and some of these went on to a fatal termination. The presence of a calculus associated with acute appendicitis presages a graver prognosis

since 80 per cent of the reported cases have been complicated by perforation or abscess formation.[7] On rare occasion the process goes still further and the stone extrudes itself through a sinus in the right lower quadrant.[12]

Chemical Analysis. Appendiceal calculi were analyzed by Maver and Wells[8] who studied 25 stones varying from 5 to 10 mm. in diameter. They state "about one-fifth of the material was organic residue, mostly vegetable fiber, indicating that some part of the appendiceal concretions at least, comes from the cecum. Probably the rest of the concretion is deposited from the

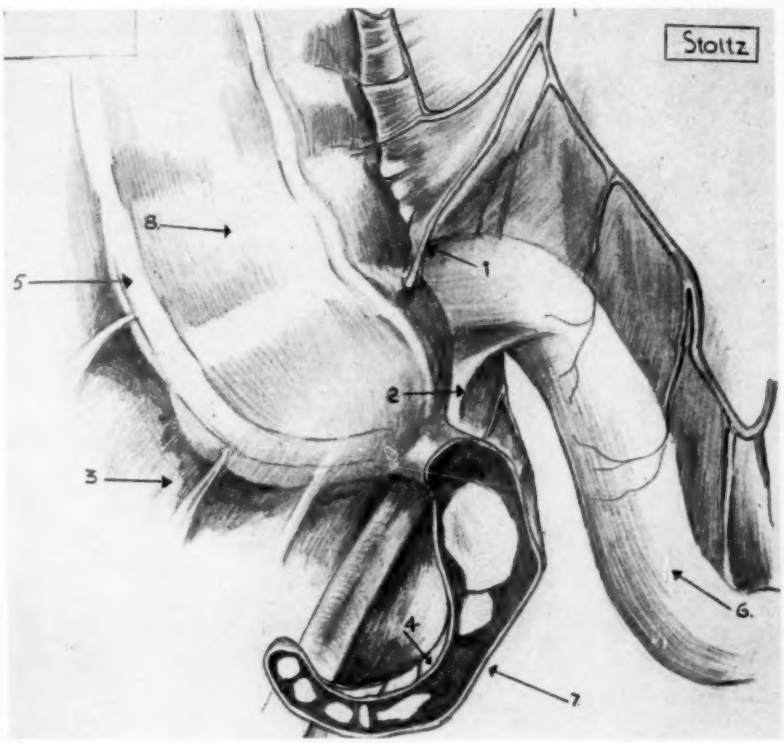


FIG. 1.—A reconstruction showing the appendix and the calculi as they looked at the time of laparotomy. (1) Ileo-colic fossa, (2) Ileo-cecal fossa, (3) Retro-cecal folds, (4) Mesoappendix, (5) Tenia coli, (6) Terminal ileum, (7) Appendix, (8) Cecum.

walls of the appendix since the bowel secretions are known to contain much fatty material and calcium." They found the calculi to contain inorganic material 25 per cent (chiefly calcium phosphate), organic residue 20 per cent (chiefly vegetable fiber), and fat soluble substances 50 per cent (coprosterol, soaps, and cholesterol). Vermooten[9] analyzed a laminated stone and found it to contain bile, cholesterol, and silicaceous material (mainly calcium phosphate).[9]

Differential Diagnosis. The following diseases in addition to appendicitis must be considered in the differential diagnosis: (1) ureteral,[11,13] renal[10] or

vesical stone; (2) cholecystitis and cholelithiasis[10]; (3) gall stone ileus; (4) phlebolith; (5) calcified mesenteric nodes; (6) retained barium; (7) calcified dermoid of the ovary; (8) calcified appendix epiploica; (9) appendiceal foreign body.[15]

Diagnostic procedures which have proved most helpful include spot roentgenograms[14] of the right upper and lower quadrants,[16] cholecystography, gastro-intestinal series and barium enema, as well as intravenous and retrograde pyelography. Pneumoperitoneum has been used as an aid when the diagnosis

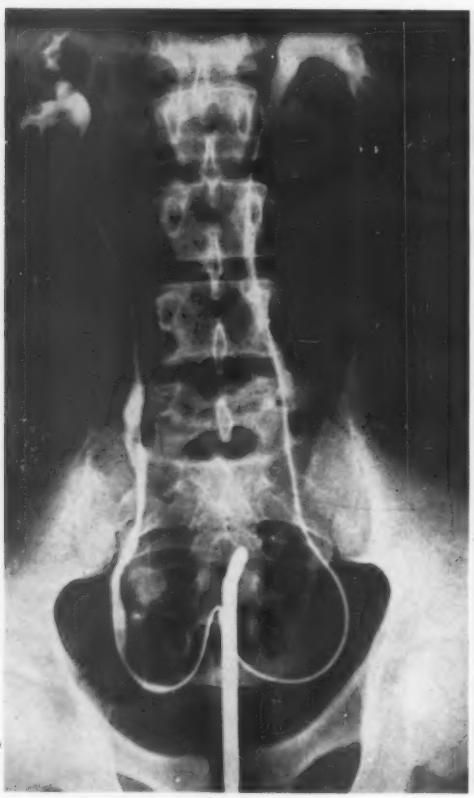


FIG. 2

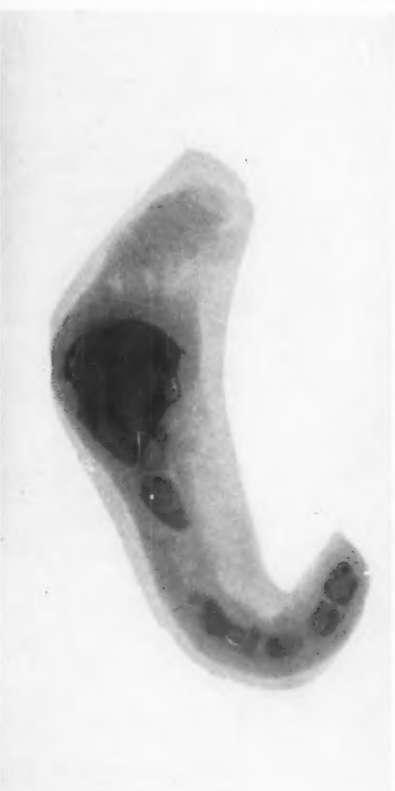


FIG. 3

FIG. 2.—A retrograde pyelogram showing the kidneys and ureters filled with radiopaque material, and in the right lower quadrant, just below the pelvic brim a calculus is visualized.

FIG. 3.—A lateral roentgenogram of the appendix after its removal.

could not be made conclusively.[10] Extraperitoneal exposure of the ureter was performed when the location of a calculus could not be determined.[11]

SUMMARY

1. A review of the reported cases of appendiceal calculi is presented, together with a description of one additional case which was diagnosed preoperatively.

2. The etiology and composition of appendiceal calculi is briefly discussed.

3. The clinical significance of these calculi in terms of perforation and prognosis is emphasized.

BIBLIOGRAPHY

1 Bunch, G. H., and D. F. Adcock: Giant faceted Calculi of the Appendix. Ann. Surg., **109**: 143, 1939.
2 Pfahler, G. E., and C. J. Stamm: Appendiceal Calculi. Surg., Gynec. & Obst., **21**: 14, 1915.
3 Stiven, H.: Radiopaque Calculus in Bilharzial Appendicitis. J. Egypt M. A., **18**: 658, 1935.
4 Jones, C. J.: Personal communication.
5 Kelly, Howard, and E. Hurdon: The Vermiform Appendix and Its Diseases. Saunders, 1905.
6 Royster: Appendicitis. D. Appleton Co., 1927.
7 Thomas, S. F.: Appendiceal Coproliths—Their Surgical Significance. Radiology, **49**: 39, 1947.
8 Maver, M. E., and H. G. Wells: The Composition of the Appendiceal Concretions. Arch. Surg., **3**: 439, 1921.
9 Vermooten, V.: Appendiceal Lithiasis. Boston M. and S. J., **193**: 718, 1925.
10 Albert, S.: Appendiceal Stones Simulating Gallstones and Kidney Stone. Radiology, **4**: 428, 1924.
11 Mark, E. G.: Appendiceal Concretions Simulating Ureteral Calculi. J. A. M. A., **83**: 1689, 1944.
12 Wells, C. A.: Appendix Concretions Opaque to X-ray. Brit. M. J., **2**: 1041, 1930.
13 Coleman, W. G.: Coprolith Simulating Ureteral Calculus. Int. Coll. Surg., **7**: 397, 1944.
14 Douglas, J., and L. T. LeWald: Fecal Concretions of the Appendix Demonstrable by X-ray. J. A. M. A., **66**: 1919, 1916.
15 Fowler: Foreign Body Appendicitis. Ann. Surg., **56**: 427, 1912.
16 Jackman, J.: Roentgen Diagnosis of Appendiceal Fecaliths. Am. J. Roentgenol., **48**: 803, 1942.
17 Tripodi, A. M., and A. L. Kruger: Appendiceal Lithiasis. Am. J. Surg., **61**: 138, 1943.
18 Pilcher, L. S.: Giant Calculus of the Appendix. New Eng. J. Med., **232**: 163, 1945.
19 Packard, H.: Appendiceal Lithiasis. Report of a Case Unique in the Annals of Surgery. Boston M. and S. J., **185**: 656, 1921.
20 Shahan, J.: An Unusual Case of Multiple Appendiceal Lithiasis. Radiology, **35**: 89, 1940.
21 Guido, F. R.: Appendiceal Calculus—Report of a Case. California and West. Med., **55**: 19, 1941.
22 Shelley, H. J.: Calcified Fecalith in the Appendix. Surgery, **3**: 658, 1938.
23 Mulleder, A.: Zentralbl. f. Chir., **1**: 384, 1923.
24 Rigollot-Simonnot and Saissi.: Paris Chirurg., **5**: 1085, 1913.
25 Jacobs: Calcul appendiculaire de 2 gr. 40 avec rupture de l'append. Bull. Soc. belge de Gynec., **20**: 114, 1909–10.
26 Downes, W. A.: Large Fecalith in the Appendix. Ann. Surg., **66**: 506, 1917.
27 Levi, D.: A Radiopaque Concretion in the Appendix. Lancet, **2**: 653, 1934.

A COMBINATION PROBE, DILATOR AND IRRIGATOR FOR COMMON DUCT SURGERY*

A. L. WILKIE, M.D.

MONTREAL, CANADA

FROM THE DEPARTMENT OF SURGERY, ROYAL VICTORIA HOSPITAL AND MCGILL UNIVERSITY, MONTREAL, P. Q.

THE MULTITUDE of instruments available for exploration of the common bile duct indicates that none fills all requirements in a satisfactory manner.

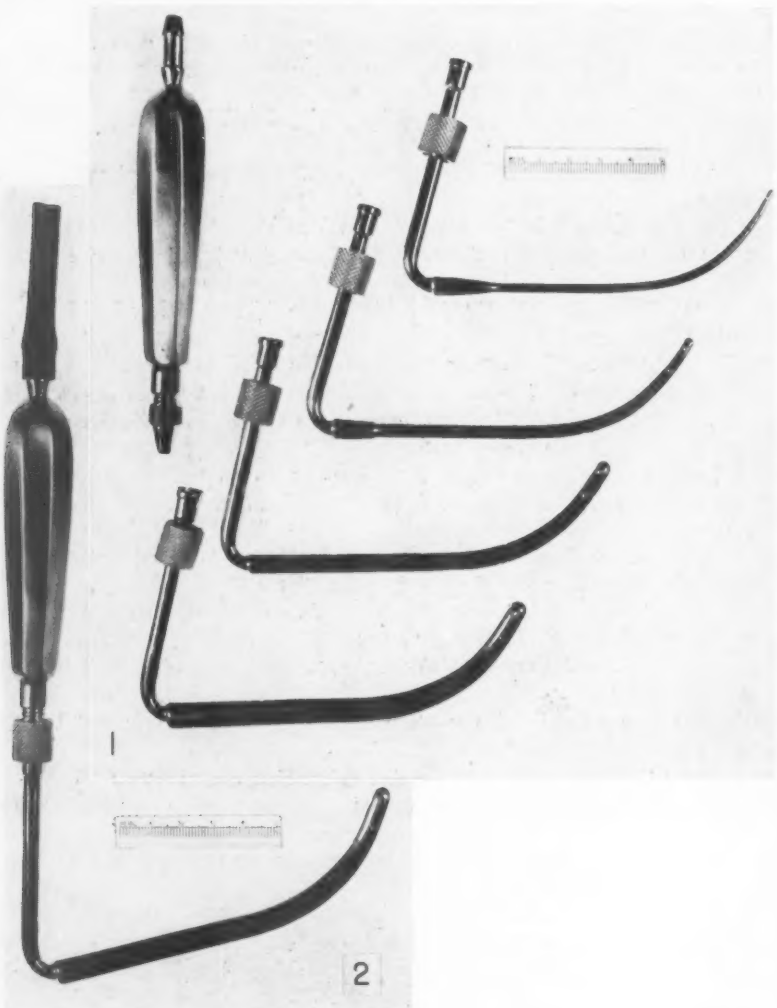


FIG. 1.—The Archibald instrument with detachable handle and graded-sized probes.
FIG. 2.—The instrument assembled.

* Submitted for publication December, 1948.

COMBINATION PROBE, DILATOR AND IRRIGATOR

The late Dr. Edward Archibald devised an instrument which has been in use in the Royal Victoria Hospital for the past 15 years. It has proved to be so simple and efficient that it is considered worth while to publish a brief description.

The instrument consists essentially of a hollow handle with a series of detachable hollow probes of graded sizes. These are designed to fit the curve of the common duct and are perforated so that irrigation may be carried out. The device can thus be utilized as a probe, irrigator or dilator (Figs. 1 and 2).

The probes are sizes 12F, 17F, 23F and 29F. These have proved to be the most useful in practice and they provide a good range for dilatation of the

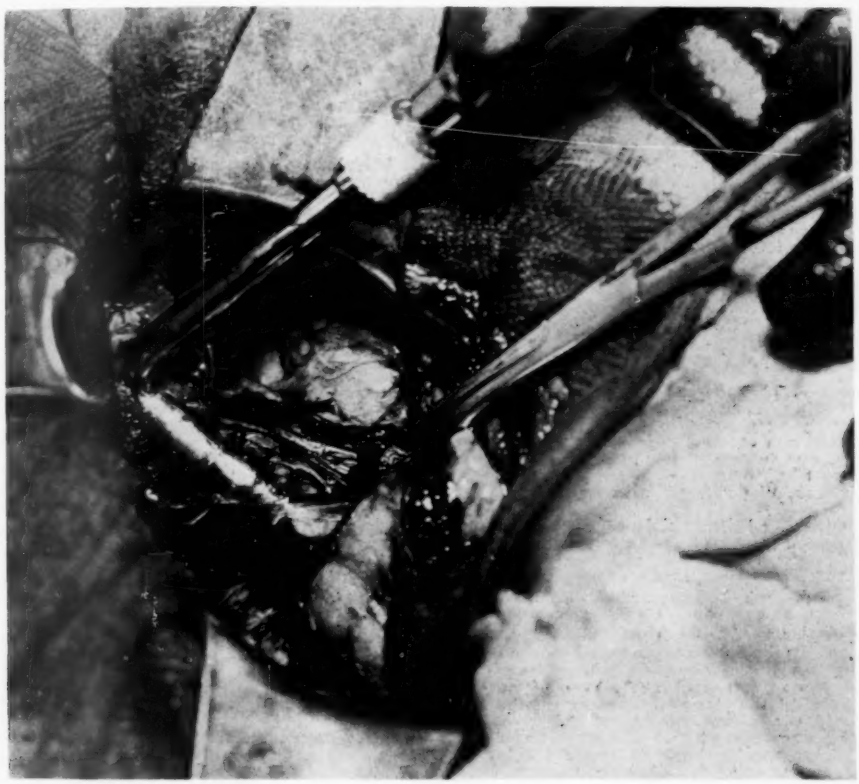


FIG. 3.—The probe in use in exploration of the common bile duct.

sphincter of Oddi. The neck of the probe is angulated 75° in order to clear the costal margin when introducing the instrument into the duct. The length is 7 cm. from neck to tip.

In the average case the probe can be introduced with the handle attached but in obese patients it is easier to insert the appropriate probe and screw on the handle in situ (Fig. 3).

A bulb syringe can be attached to the handle and saline irrigated through the probe.

It is usually possible to pass the smallest size into the duodenum and if the sphincter of Oddi is tight or the seat of a stricture it can be gently dilated with the successive sizes. We have found this instrument to be far superior to any other which has been used in the Royal Victoria Hospital. It has stood the test of time and appears to be a worth-while addition to the armamentarium of biliary-tract surgery.

STATEMENT OF THE OWNERSHIP, MANAGEMENT, CIRCULATION, ETC., REQUIRED BY THE ACT OF CONGRESS OF AUGUST 24, 1912, AS AMENDED BY THE ACTS OF MARCH 3, 1933, AND JULY 2, 1946. Of ANNALS OF SURGERY, published monthly at Philadelphia, Pa., as of November 1, 1949.

State of Pennsylvania }
County of Philadelphia } *ss.*

Before me, a Notary Public in and for the State and county aforesaid, personally appeared J. R. Arnold, who, having been duly sworn according to law, deposes and says that he is the Treasurer of the ANNALS OF SURGERY and that the following is to the best of his knowledge and belief, a true statement of the ownership, management (and if a daily paper, the circulation), etc., of the aforesaid publication for the date shown in the above caption, required by the Act of August 24, 1912, as amended by the Acts of March 3, 1933 and July 2, 1946, embodied in section 537, Postal Laws and Regulations, printed on the reverse of this form, to wit:

1. That the names and addresses of the publisher, editor, managing editor, and business managers are: Publisher, J. B. Lippincott Company, E. Washington Square, Philadelphia, Pa. Editor, Dr. John H. Gibbon, Jr., Chairman Editorial Board, 1025 Walnut St., Philadelphia, Pa. Managing Editor, Loraine Stauffer, E. Washington Sq., Phila. 5, Pa. Business Manager, Laurence S. Whyte, E. Washington Square, Philadelphia 5, Pa.

2. That the owner is: (If owned by a corporation, its name and address must be stated and also immediately thereunder the names and addresses of stockholders owning or holding one per cent or more of total amount of stock. If not owned by a corporation, the names and addresses of the individual owners must be given. If owned by a firm, company, or other unincorporated concern, its name and address, as well as those of each individual member, must be given.) J. B. Lippincott Company, E. Washington Square, Philadelphia, Pa.; Ellis W. Bacon, Wallingford, Pa.; Sarah L. Biddle, Bethayres, Pa.; Bertram Lippincott, Penllyn, Pa.; Cross & Co., Philadelphia, Pa.; J. W. Lippincott, Bethayres, Pa.; Estate of Marianna L. O'Neill, Rydal, Pa.; Pennsylvania Company for Insurances on Lives and Granting Annuities, Trustee Estate of Craige Lippincott, Philadelphia, Pa.; Fidelity Philadelphia Trust Company, Trustee Estate of Walter Lippincott, Philadelphia, Pa.; Howard K. Bauernfeind, Wynnewood, Pa.; George Stevens, Kingston, N. J.

3. That the known bondholders, mortgagees, and other security holders owning or holding 1 per cent or more of total amount of bonds, mortgages, or other securities are: None.

4. That the two paragraphs next above, giving the names of the owners, stockholders, and security holders, if any, contain not only the list of stockholders and security holders as they appear upon the books of the company but also, in cases where the stockholder or security holder appears upon the books of the company as trustee or in any other fiduciary relation, the name of the persons or corporation for whom such trustee is acting, is given; also that the said two paragraphs contain statements embracing affiant's full knowledge and belief as to the circumstances and conditions under which stockholders and security holders who do not appear upon the books of the company as trustees, hold stock and securities in a capacity other than that of a bona fide owner; and this affiant has no reason to believe that any other person, association, or corporation has any interest direct or indirect in the said stock, bonds, or other securities than as so stated by him.

[Signed] J. R. ARNOLD.

Affirmed to and subscribed before me this 3rd day of October, 1949.
[Seal] HARRY J. BEARD.

(My commission expires March 5, 1953.)

Editorial . . .

Diverticulitis of the Colon

Diverticulosis of the colon is a common condition among individuals of both sexes over the age of 50. It is now being recognized that a variable degree of diverticulitis occurs in almost all of these cases. Fortunately for the purposes of surgical treatment, in a very large percentage the diverticula are confined to the sigmoid and lower descending colon. In the cases of diverticulitis requiring surgical therapy this is equally true, over 85 per cent of the lesions being confined to this area. Thus, complete excision of the local lesion may be carried out if surgical intervention should be required.

Although the disease most often follows a fairly definite course, the future of any individual case is quite unpredictable. Thus the progress of the inflammatory changes, although usually slow, may be rapid; complications, which ordinarily occur late, may appear at an early stage. Therefore, once recognized, each case must be followed carefully by the general physician and re-examined at regular intervals.

For many reasons the medical profession at large has adopted a rather inert and ultra-conservative attitude towards the surgical therapy of this condition. This attitude often results in the continuance of palliative treatment long after definite danger signals have appeared and in many instances the condition is allowed to progress to a stage where definitive surgical therapy is both difficult and hazardous, if not impossible. There appear to be many factors responsible for this state of mind, the following probably being the most important:

First, the slow progress of the disease and the relatively small number of cases which ultimately require operative therapy.

Second, advanced inflammatory changes may be present in the colon without causing proportionate signs and symptoms, so that often the physician is unaware of the stage of the disease and the imminence of complications.

Third, the fact that it is generally believed (and probably rightly so) that diverticulitis is not a forerunner of cancer. There is not sufficient awareness, however, that in the late stages it is difficult and often impossible to distinguish cancer from diverticulitis by any means.

Fourth, this attitude seems in part to be a legacy from the past when the results of operative interference were often very poor. It is only within relatively recent years that the general acceptance of defunctioning colostomy and the availability of potent antibiotics plus many other important concurrent advances in surgical knowledge have made definitive surgical therapy reasonably safe.

Fifth, the formidable nature of the operative treatment, comprising, as it most frequently does, a colostomy and multiple operations covering a period

of a minimum of six months, weighs heavily in the minds of both patient and physician.

In the past, surgical treatment was not considered to be indicated unless one or more of the following complications were present: severe unremitting obstruction, perforation with its secondary sequelae, or fistula formation. This attitude towards surgery still persists, and consequently when many patients are finally referred to the surgeon the condition has advanced to a stage where operative cure is virtually impossible. What is needed is general recognition of the excellent results of properly timed operative treatment and a clearer knowledge of the indications for operation. It is not necessary at the moment to give these in detail, but speaking generally, it may be said that in the second stage of the disease, where irreversible inflammatory changes are present in the colon, if a patient should continue to suffer with moderate or severe attacks of diverticulitis *in spite of adequate palliative therapy*, then surgical treatment should be advised.

There are several features of the surgical therapy of this condition which are of great interest and the subject of considerable discussion. Among these are the following: the place of colostomy as definitive treatment with subsequent closure without excision of the affected area; primary resection of the colon with or without complementary colostomy, the formation of a colostomy at the time of laparotomy for local or diffuse peritonitis following perforation; and the necessity or otherwise of excision of all the diverticula. At this time all that can be offered in regard to these problems is that in general in this condition, because of the infective process and the possibility of poor healing, all safety factors should be observed. Fixed routine methods of treatment are dangerous. Each case must be decided completely upon its individual merits.

As has been indicated in the foregoing, it is felt that persistence of the inert and ultra-conservative attitude of the past towards the surgical therapy of diverticulitis is responsible for much of the morbidity and mortality that still attends treatment. Properly timed surgical therapy gives such comparatively excellent results that it is imperative that the profession at large gain a clearer understanding of the danger signals of impending complications and advise operative interference at an earlier stage.

FREDERICK I. LEWIS.